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THE FORMATION AND MOVEMENTS OF LYMPH

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ALL who deal with the physiology of the body fluids encounter again and again the problem of the nature and composition of the extravascular environment. Four fluids must be considered as involved in the problem. They are (1) the blood plasma, (2) the capillary filtrate, (3) the tissue fluid, and (4) the lymph.

I believe that there is no longer serious debate as to the fact that typical normal blood capillaries, such as those in the skin and in the subcutaneous tissue, are somewhat permeable to serum albumin and serum globulin. These proteins are normal constituents of lymph wherever it is collected, and there can be no doubt that they filter from the blood capillaries practically all over the body. I pointed out, in 1933, that where capillaries are structurally specialized, as in the glomeruli and the choroid plexuses, the capillary membrane is in reality a two-layer affair, and does not resemble the typical capillary with its single layer of endothelial cells.

At the same time, capillaries have been held to vary greatly in permeability; this idea is based largely upon differences in the composition of lymph from different regions. For example, in Table I there are four estimations of protein in blood and in liver lymph. No other lymph in the body shows such high protein concentrations as these, but I am by no means sure that this is not a concentration phenomenon due to the extensive water requirements of the liver. We used to believe that a large fraction of the highly proteinized thoracic duct lymph came from the liver, but Markowitz and Mann[1] (1931), in experiments in which they were collecting thoracic duct lymph from dogs, found no diminution in the volume of this lymph after ligation of the periportal lymphatics, or even after removal of the liver. There

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is little doubt that in the quiescent, anesthetized animal at least 90 per cent of the thoracic duct lymph comes from the intestines. This lymph is rich in protein, and there has been much talk about the high degree of permeability of the intestinal capillaries. I am inclined to

TABLE I

PROTEIN CONCENTRATION IN BLOOD AND IN LIVER LYMPH FROM FOUR DOGS

DOG	TOTAL PROTEIN IN GRAMS PER CENT	
	BLOOD SERUM	LIVER LYMPH
1	7.64	6.20
2	6.16	4.45
3	5.91	5.56
4	5.66	5.10

think that this opinion rests on failure to realize the mechanical conditions which affect the circulation in the gut. Examine, for example, Mall's (1896) reconstruction of the blood vessels and lymphatics in the wall of the stomach, as seen in Fig. 1; considered mechanically, the same conditions recur through the entire intestinal tract. Observe that the arteries and veins supplying the very profuse network of blood capillaries must pass through heavy layers of muscle before ramifying as capillaries. I cannot present direct evidence as to pressures, but the arrangement clearly suggests the possibility that during peristaltic contractions venous pressure and, consequently, capillary pressure may rise. At the same time lymph will be squeezed toward the thoracic duct. The arrangement is beautifully adapted for the production and movement of lymph, so much so as to make one wonder whether the very profuse supply of intestinal capillaries consists of vessels which are specially permeable, or whether what has been interpreted as excessive permeability is not simply the expression of the physiologic setting in which the capillaries reside. So, in considering the permeability of capillaries, one can never think in terms of a simple membrane appropriately mounted for filtration in the chemical laboratory. It is necessary, first, to think of the histologic character of the membrane, whether it be reenforced, as in the glomeruli, or possibly latticed, as in the case of the spleen. Second, one must examine the setting of the capillaries, whether they are subjected, as in the gastrointestinal tract, to mechanical influences calculated to alter pressures in such a way as to produce filtration. Third, one must take into account a long list of chemical and physical conditions which have been held to affect filtration and attempt to decide whether they alter the membrane, or whether they alter pressure relations, and thereby induce greater filtration through an unchanged membrane. The most important of such conditions are the following:

1. Oxygen lack and carbon dioxide increase.
2. Activity of the tissue under observation.

3. Miscellaneous chemical and hormonal effects, such as the possible production of histamine, and such hormonal factors as those which influence the oestrus edema of the sexual skin in monkeys.
4. Increase and decrease of plasma protein concentration.
5. Temperature.
6. Capillary blood pressure.
7. Tissue pressure.
8. Contraction and dilatation of capillaries.
9. Arteriovenous anastomoses.

All of these factors, except the last, have large places in the literature of capillary permeability. The possible relation of arteriovenous anastomoses to capillary filtration is just beginning to be appreciated. These anastomoses were described in 1877 by Hoyer,[2] then forgotten, and now are moving into physiologic prominence after a period of extensive and profitable anatomization.

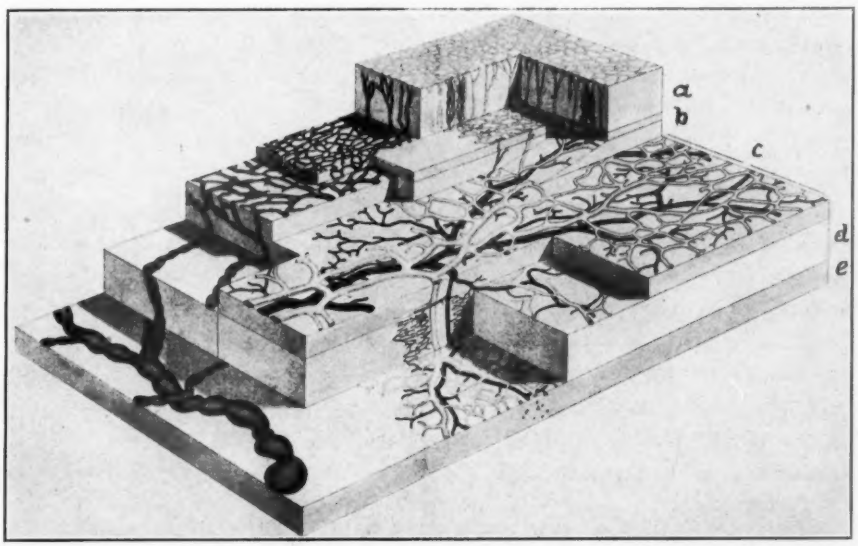

Fig. 1.—Reconstruction of a small portion of the middle zone of the stomach. The long diameter of the drawing is in the direction of the longitudinal muscle fibers. It was built up from 36 drawings, and each drawing is an exact representation of a specimen. Enlarged 20 times. *a*, mucous coat; *b*, muscularis mucosae; *c*, submucous coat; *d*, circular muscle; *e*, longitudinal muscle. (From Mall, F.: The Vessels and Walls of the Dog's Stomach, Johns Hopkins Hospital Reports 1: 1, 1896.)

They would seem to present a beautiful mechanism for preventing excessive capillary pressures when blood flow is extremely rapid. Let us consider an individual exercising violently. Capillary blood flow is enormously increased in order to provide the necessary oxygen, but excess pressure in the capillaries is in all probability prevented by opening of the arteriovenous by-passes. All of us who have perfused isolated organs have learned to use a by-pass of varying resistance in order to prevent excess pressures. In regard to filtration

from the capillaries, the arteriovenous anastomoses, when widely open, may thus be thought of as lessening the pressure head in the capillaries and increasing the load upon these vessels if they are contracted.

The admission that normal capillaries leak the blood proteins illustrates the usual plight of the physiologist. It simply pushes him on to another question: How permeable are the capillaries to protein, or, to put it in a more practical fashion, what is the nature of the capillary filtrate? Efforts to answer this question have been of two types. First, there have been attempts to cause increased capillary filtration, and then calculate the probable protein concentration of the filtrate. A noteworthy example of such experiments is that of Landis, Jonas, Angevine, and Erb[3] (1932). They declared that the capillary filtrate in the human arm contained not more than 0.3 per cent of protein. Figures for the protein concentration of normal peripheral lymph are extremely few. Some years ago, White and I cannulated an ankle lymphatic in my associate, Miss Field. She walked about with the cannula in place, and the lymph produced contained 0.49 per cent of protein. This is a low figure, but it is certain that the fluid escaping from the blood capillaries is concentrated either where it passes out, or in a lymphatic trunk before it can be collected for analysis.

The second method of determining the nature of the capillary filtrate consists in the measurement of the protein content of edema fluid, particularly in cases of cardiac edema. Bramkamp[4] (1935) provides a fairly recent example. In twenty-six patients with the edema of congestive heart failure, the protein varied from 0.03 to 0.54 per cent. In such persons reabsorption of water is considered not to occur, and the edema fluid is thus not only capillary filtrate but tissue fluid at the same time. It appears right to make this assertion for the conditions in question, but reabsorption of water is not prevented under normal conditions in healthy persons, and there is no valid reason to believe that concentration of extravascular fluid does not occur.

Again we are confronted by a question. If concentration of extravascular fluid occurs, are tissue fluid and lymph affected alike, or is concentration more prominent in one than in the other?

Actual collection of tissue fluid in the normal mammal has never been accomplished, but recently Maurer[5] (1938) has succeeded in collecting tissue fluid from frog muscle. His method consisted in piercing the muscle longitudinally with a fine capillary tube. By an ingenious technique, he showed that because of the toughness of the sarcolemma the capillary invariably passed between muscle cells and did not wound them. When the tube was withdrawn it contained clear, straw-colored fluid, uncontaminated with blood. In nine samples of this tissue fluid Maurer found that the protein varied between 0.44 and 3.54 per cent,

with an average of 1.53 per cent. With Churchill and Nakazawa[6] (1927), I found that the protein in the lymph of sixty frogs varied between 0.29 and 2.17 per cent, with an average of 1.0 per cent. The agreement is close enough to enable one to say that in the single instance in which tissue fluid has been obtained it is identical in composition with lymph. If such were found to be the case in the mammal, then lymph, which can be collected from many parts of the body and from isolated organs, such as the heart, would become an important instrument for physiologic analysis, in that it would really reflect the environment of the body cells.

But in the mammal the best direct evidence for the identity of tissue fluid and lymph is offered by studies in which, as edema develops, permitting the collection of tissue fluid, lymph has been obtained from the same part. Examples of such determinations are found in Tables II and III.

Several years ago we (Drinker, Field, and Homans,[7] 1934) produced fairly complete obstruction of the lymphatics in the leg of the dog. Lymphedema develops slowly in such animals, and as it begins to appear a puncture wound will provide clear edema fluid. At the same time one may cannulate an ankle lymphatic and collect lymph. Table II presents data obtained in this way from four dogs. There is obviously close agreement between the values for protein concentration in the two fluids. Weech and his associates (1934)[8] made precisely similar observations upon dogs rendered edematous by plasmapheresis, or by protein deprivation, which are listed in Table III. Again there is agreement in protein values.

Whether or not lymph and tissue fluid are reasonably identical in composition must continue to be the subject of experiment, and direct experiment if possible. But whatever the final result may be, there

TABLE II

SIMULTANEOUS PROTEIN VALUES IN LYMPH AND EDEMA FLUID FROM THE FEET OF DOGS RENDERED EDEMATOUS BY LYMPHATIC OBSTRUCTION

NO. OF ANIMAL	DATE	LYMPH PROTEIN (%)	EDEMA FLUID PROTEIN (%)
1	9/15/33	3.37	3.37
	4/ 3/34	2.48	3.45
2	4/ 9/34	2.55	1.86
3	2/25/33	2.67	2.00
	3/ 8/33	2.45	2.20
4	3/28/33	2.28	2.75
	5/ 5/33	2.97	3.17
	10/16/33	3.17	3.17
	4/ 6/34	2.50	2.67

can be no doubt that lymph is formed from the extravascular tissue fluid, and the state of this fluid in the tissues is thus a matter of consequence for us. All varieties of experiment show that in normal tissues

very little free fluid exists. A hypodermic needle thrust beneath the skin produces nothing. No one who has worked upon the physiology of lymph formation and movement in vessels other than the thoracic duct has ever failed to be annoyed by the small amounts of lymph obtained.

TABLE III

COMPARATIVE PROTEIN CONTENTS OF EDEMA FLUID AND THE LYMPH COLLECTED IMMEDIATELY AFTER CANNULIZATION

(From Weech, Goetsch, and Reeves[8])

DOG NO.	HIND LEGS				FORE LEGS				ASCITIC FLUID	NATURE OF EDEMA
	RIGHT		LEFT		RIGHT		LEFT			
	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH	EDEMA FLUID	LYMPH		
	per cent	*per cent*	*per cent*	*per cent*	*cent per*	*per cent*	*per cent*	*per cent*	*per cent*	
5	0.23	0.18								Nutritional
8-40	0.04		0.02	0.11					0.02	Nutritional
8-06	0.17	0.28	0.14	0.60		0.31		0.23	0.13	Nutritional
8-38	0.08	0.53		0.30		0.29			0.32	Nutritional
9-92						0.07		0.06	0.01	Plasmapheresis
6						0.32		0.15	0.03	Plasmapheresis
5-8	0.09	0.06	0.08							Plasmapheresis
9-1	0.86*	0.38	0.95*							Plasmapheresis
2-3			0.17	0.19	0.16	0.14				Nutritional
1-31	0.04	0.01	0.16*						0.01	Plasmapheresis

*These edema fluids contained blood.

Observations such as these have caused it to be held that the tissues contain no free fluid, that the extravascular environment is a sort of gel (Clark and Clark,[9] 1933). While I am in absolute agreement with the conception that there is little free water in the tissues, I do not see how they can resemble a gel. One may thrust needles into gelatin as long as one pleases, and no water will escape, even though the gelatin is quite fluid. Also, if there is no free fluid in the tissues, how does one account for the fact that though lymph is ordinarily small in amount, still it is there, and no one has ever demonstrated glandular activity for lymphatic endothelium, secretory ability such as is possessed by the salivary glands in abstracting water and other substances from the blood. The formation and composition of lymph depend on the status of the tissue at the moment. Thus, Field and Drinker[10] (1931) found that the protein content fell and the rate of lymph flow rose promptly when dogs were subjected to acute plasmapheresis, and Haynes[11] (1932) showed that immediately after severe hemorrhage lymph flow fell and lymph protein became more concentrated.

As far as I can see, all evidence indicates that the lymph keeps closely in touch with the extravascular environment, and the prime function of the lymphatics is to remove extravascular protein which in their absence accumulates and leads to edema. The lymphatic endo-

thelium is apparently very permeable to the blood proteins and to many things of even larger size which do not enter the blood when deposited in the tissues.

The formation of lymph is thus, first of all, dependent upon the amount of free fluid in the tissues, and, second, upon influences which empty draining lymphatics and permit further absorption of raw material by lymphatic capillaries. Let me illustrate by picturing the situation in the skin and subcutaneous tissues when edema occurs. If histamine is injected into the skin, edema occurs rapidly and the free fluid in the tissue is at once increased. In the loose connective tissue one sees separation of fibers, and on careful observation it soon becomes apparent that the lymphatics are becoming dilated. Pullinger and Florey[12] (1935), whose work is shown in Fig. 2, found that lymphatic capillaries are attached to surrounding tissues. When edema occurs, though tissue pressure may be increased, they are pulled open, and the permeability of their walls for the constituents of the edema fluid causes them to fill with it. If edema formation is abrupt and continuous, the mere fact of its existence may produce lymph flow from trunks draining the part. Some years ago we cannulated an ankle lymphatic in a dog and then dipped the foot in very hot water for two minutes. The foot swelled rapidly, and lymph which was practically blood plasma flowed in a steady stream from the cannula, which was placed well above the lesion. But to secure an increase in lymph flow from edema alone one needs a rapid, marked increase in tissue pressure, and in the ordinary congestive edema this does not occur. If, however, the edematous part is massaged or moved actively or passively, lymph flow will be more rapid than normal. The bedridden patient with cardiac edema delivers exceedingly little edema fluid back to the circulation via the lymphatic system. Only by movement or massage can any impression be made.

Too much of our information upon the normal movements of lymph has been based on data concerning the flow from the thoracic duct in quiescent, anesthetized animals. Under such circumstances practically all of the lymph collected comes from the gastrointestinal tract and from the heart. It is usually thought that one obtains very little thoracic duct lymph unless the animal is digesting fat. This is not so. The thoracic duct lymph owes its volume to the intestinal blood capillaries which supply the water and the protein of the lymph. The actual volume of fat absorbed is small; in fact, one often gets the largest volumes of thoracic duct lymph after fat deprivation. A good circulation and active peristalsis are the factors which cause free movement of lymph from the intestine.

Of greater interest to us are the ordinary movements of lymph in such regions as the skin. The extent of the lymphatic capillary system

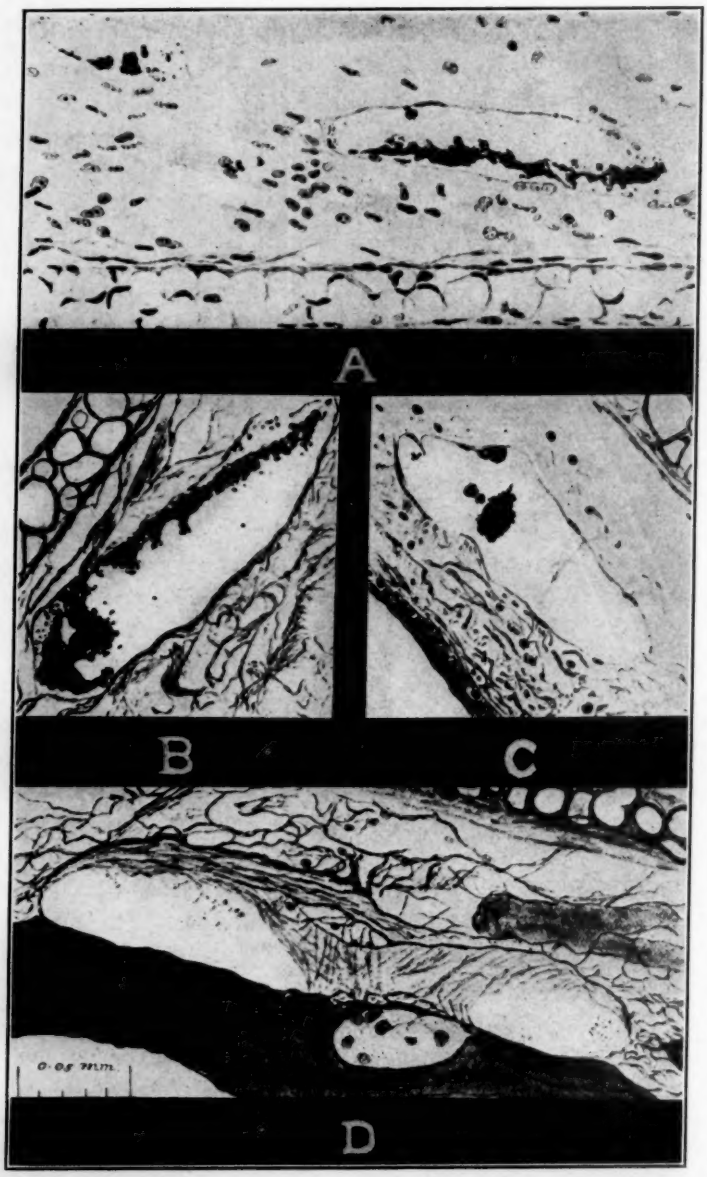

Fig. 2.—*A.* Histamine edema in mouse's ear. Widely opened lymphatics containing hydrokollag, superficial to skeletal muscle bundles. Connective tissue fibers attached to walls. Stained with iron-hematoxylin and van Gieson. *B.* Histamine edema in mouse's ear. Deep lymphatic near central cartilage, widely open, containing hydrokollag and with connective-tissue fibers attached to walls. Silver impregnation. *C.* Histamine edema in mouse's ear. Superficial lymphatic containing hydrokollag, widely dilated. Wall attached to collagen fibers in the corium. Stained with azan. *D.* Superficial lymphatic in edematous ear in a section 14μ thick, showing wall, cut tangentially, composed of interlacing fibers of collagen and reticulum. Silver impregnation. The dark mass at the bottom is skin epithelium. (From Pullinger and Florey[12].)

in the skin is little appreciated. Fig. 3 is a reconstruction of the capillary lymphatics of the skin. There are two plexuses, a superficial one just beneath the epithelium, containing few valves, and a second in the deeper part of the corium and in the subcutaneous areolar tissue beneath it. The two plexuses communicate freely and empty into large valved trunks which are found close to the veins. The arrangement is, in effect, an enormous superficial net containing very few valves in the outer part, and continuous all over the body. In the outer plexus lymph will move in any direction decreed by gravity, by motion, or by massage. The difficulty of obstructing the superficial network is obvious enough. Nothing short of complete destruction will accomplish it. The anatomic arrangement makes it

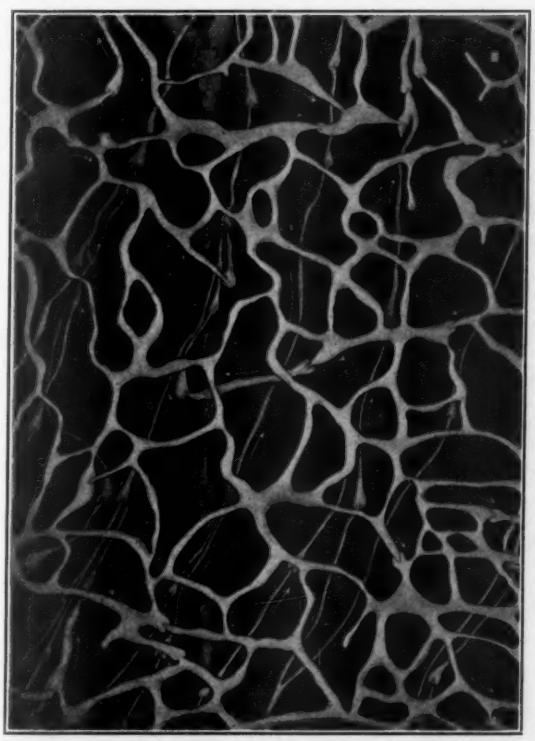

Fig. 3.—Reconstruction of a small portion of the lymphatic plexus in the cutaneous and subcutaneous area of the leg of a 130-mm. (4.3 months) fetus. ×66⅔. White rectangle in the upper corner indicates natural size of the area shown. Note the numerous valves, and the drainage of the subcutaneous plexus into the deeper, more regularly disposed, and more slender lymph channels. *v.s.*, vena saphena magna. (From Kampmeier, O. F.: The Genetic History of the Valves in the Lymphatic System of Man, Am. J. Anat. **40**: 413, 1928.)

clear that if one gets obstruction of the deeper lymphatics in a part, it is still sometimes possible to discover superficial vessels; and if the part is massaged or given opportunity to drain by gravity, lymph may find its way in the meshwork as the external force directs it.

Recent work (Forbes,[13] 1938) indicates that there is free communication between skin lymphatics across the midline of the body and gives no indication that local areas are separated from other parts, as has often been thought.

It is easy to collect skin lymph from a cannulated ankle lymphatic in a dog. In Fig. 4 the position of the cannula is shown. It is inserted under local anesthesia, and then the dog may walk or run quite normally for many hours. When he lies quietly no lymph flows from the cannula. When he walks at a uniform rate lymph flow soon becomes quite steady. I[14] described different facts learned by means of this preparation in a Harvey Lecture last year and will not review the material again, but I do wish to point out one thing. If we cause such an animal to walk until lymph flow becomes constant, and then permit him to rest for half an hour before again walking at the same rate, he will invariably begin the new period of movement with a large flow of lymph which will decrease as walking continues. When he lies still no lymph leaves the part, and fluid apparently accumulates until tissue pressure balances filtration pressure. Under these circumstances water and crystalloids may be absorbed by the blood capillaries and replaced from them, but, after a time, loss of protein from the capillaries must be slight. As soon as the animal walks, tissue fluid and lymph are caused to enter and move in the lymphatics, and capillary filtration may again become active.

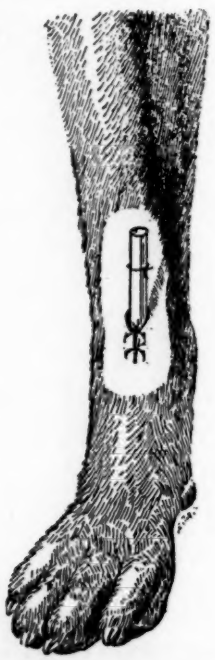

Fig. 4.—Front leg of dog with cannula in a collecting lymphatic and tied to the skin. (From Drinker, C. K., and Field, M. E.: Lymphatics, Lymph and Tissue Fluid, Baltimore, 1933, p. 89, Williams and Wilkins Company.)

During the past winter we have made a new preparation which permits us to obtain lymph in a normal manner from anesthetized animals

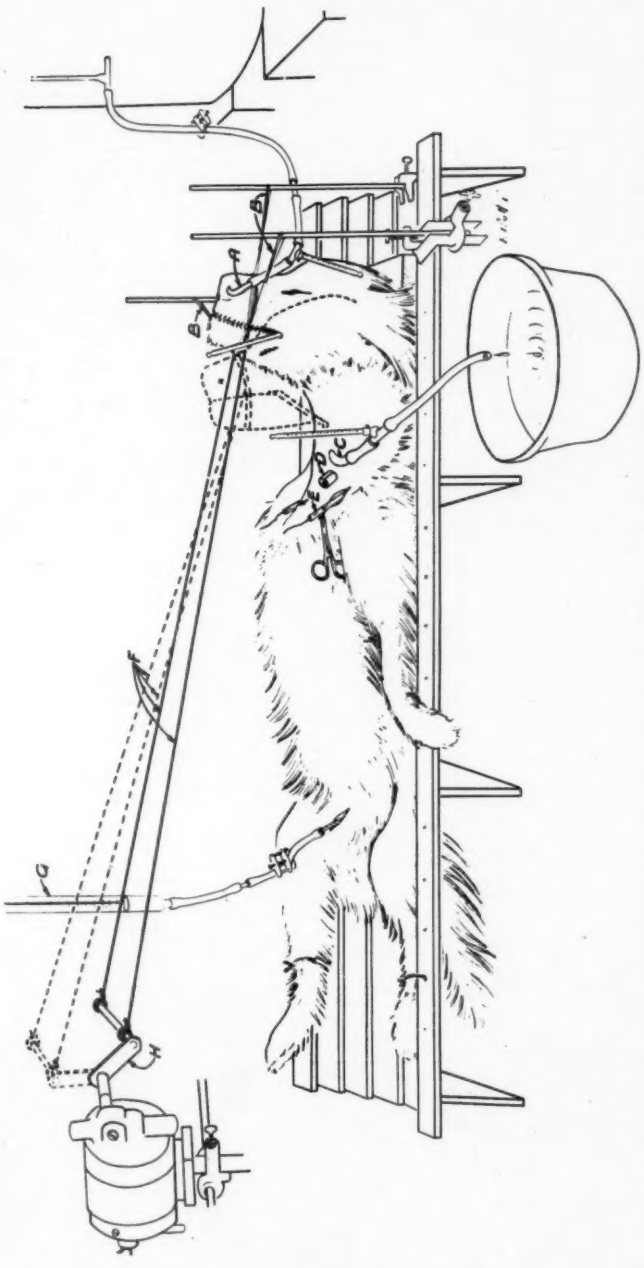

Fig. 5.—Diagram of apparatus for passive motion of the head and perfusion of the nasopharynx. *A*, inflow perfusion tube from constant temperature reservoir to nostril; *B*, rubber bands; *C*, outflow perfusion tube tied into trachea; *D*, tracheal cannula; *E*, cannulae in cervical lymphatics; *F*, twine attaching snout to crank; *G*, burette attached to cannula in femoral vein; *H*, electrically driven crank. When the motor rotates the crank, *H*, the head is flexed, and the rubber bands, *B*, return it to the usual prone position. This slight passive motion results in a constant flow of cervical lymph and produces ideal conditions for studying the absorption of various substances from the nasopharynx. (From McCarrell[15].)

(McCarrell,[15] 1939). Lymph in this case is obtained by cannulating both cervical lymphatic trunks at about the middle of the neck. By exclusion, we have determined that most of the lymph obtained comes

from the nasopharyngeal mucosa. We have used the preparation to study lymphatic absorption from the surface of the nasopharynx, but it applies to much besides. After the lymphatics have been cannulated, a cannula (*D*, Fig. 5) is placed in the trachea, and an L tube (*C*, Fig. 5) is inserted in the trachea above it. The snout of the dog is now attached to a rotating bar, and by elastic bands to uprights upon the animal board. Under anesthesia and quiescence one obtains little or no cervical lymph from the dog; but if the rotator operates, the head nods deliberately ten times a minute and lymph flows steadily from the cannulated vessels as long as one cares to make observations. Many things may be accomplished. For example, suppose a catheter is inserted in the nose. Physiologic salt solution, at any temperature, with any sort of addition one pleases, may be irrigated through the nasopharynx and out of the L tube in the trachea. In Fig. 6 is displayed the type of information which may be elicited. The upper curve gives the protein concentration of the lymph in per cent, the middle curve the volume of lymph per minute in milligrams, and the lower curve the lymph protein in milligrams per minute. After a period of about forty-five minutes,

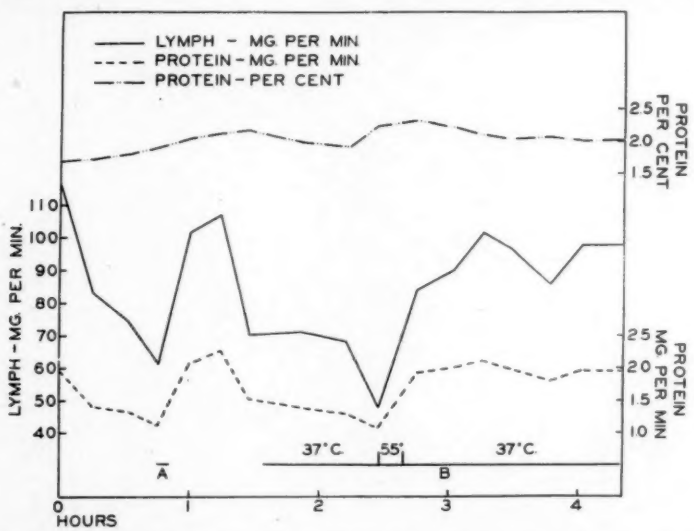

Fig. 6.—Chart illustrating sensitivity of method. The upper curve shows the percentage of protein in the pooled lymph from both cervical ducts of a dog. In the lower curves are charted the total amounts of lymph and of lymph protein collected per minute. During *A*, the external jugular veins were clamped for six minutes; during *B*, the nasopharynx was perfused with Ringer's solution at the temperatures indicated. Note the changes in cervical lymph flow and in protein content caused by the increase in venous pressure and by the local application of heat (55° C.). (From McCarrell[15].)

during which lymph flow falls, as is always the case when activity succeeds quiescence, the two external jugular veins were clamped in order to produce an increase in capillary pressure. Observe the immediate effect upon the volume of lymph and upon the amount of protein collected. The nasopharynx was then irrigated with Ringer's solution at

37° C. This had no effect, even though the irrigation was continued for almost an hour. But when the temperature of the irrigating solution was increased to 55° C., there was an immediate and permanent increase in lymph production. This expresses capillary injury. Water at 55° C. can be taken in the mouth, but it is at the very limit of endurance, and there is no doubt that under the circumstances of the experiment the capillaries have been damaged.

If heat is applied, gradually increasing lymph formation begins at about 42° C., and changes not readily reversible begin to appear around 50° C. The lesson of such experiments is simple enough. One can expect decided increases in tissue fluid with tissue temperatures around 42 to 45° C., just about the limit of one's tolerance for heat. If it is of advantage therapeutically to increase both the vascular and extravascular circulation, then it is obvious that a part should be heated and at the same time massaged mechanically or moved passively.

As physicians interested in the circulation I believe you will be interested in a final phase of the problem. In studies upon lymph it is always difficult to obtain material which comes from a single tissue. Recently we have been able to do this in the case of the heart. It is a fortunate circumstance for the physiologist that the lymphatic drainage of the heart concentrates between the superior vena cava and the innominate artery, where cannulation may be accomplished. The result gives part of the lymph coming from the heart. Table IV shows that the rate of lymph flow and the composition of the lymph are closely related to the degree of cardiac activity, and I believe that through heart lymph we may possess a new instrument for uncovering the physiology of the heart, both in health and in disease.

TABLE IV

CARDIAC LYMPH

TIME P.M.	AMOUNT OF LYMPH MG. PER MIN.	PROTEIN MG. PER MIN.	PROTEIN PER CENT
12:25	6.61	2.10	3.33
12:40	18.70	5.10	2.73
12:55	30.09	7.82	2.60
1:10	21.51	5.59	2.60
1:25	18.13	4.68	2.58
1:40	16.64	4.44	2.67
1:55	16.12	4.43	2.75
2:10	16.73	4.53	2.71
2:55	14.60		
3:10	20.49		
Average	18.36	4.84	2.75
3:10-3:20	Adrenin injected into jugular vein		
3:25	63.40	17.43	2.75
3:40	57.94	17.38	3.00

In conclusion, let me point out that I have been describing direct experiments on a part of the circulation which has been too much neglected, or has been the subject of calculations and deductions through indirect methods. It is a system acknowledged to play a potent part in disease, but few clinicians have knowledge even of its anatomic extent. I have been much honored in being permitted to call your attention to the possibilities of thinking in terms of the lymphatics, and hope that my introduction may lead to offspring in the shape of contributions to the clinical physiology of the lymphatic apparatus, in addition to your regular productions upon the circulation of the blood.

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THE CORONARY ARTERIES OF THE DOG

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BEFORE experimenting on the coronary circulation it is necessary to become familiar with its anatomic peculiarities. With this purpose in mind, I performed numerous dissections in the dog and found certain things which were not in agreement with previous descriptions of the coronary arteries in this species. Since the dog is much used at this time for experiments of this nature, I thought it might be worth while to publish my observations, with a concise but complete description of the anatomy of the coronary arteries of the dog.

TECHNIQUE

The heart was removed immediately after death; its cavities were washed out with tap water; and it was placed in the refrigerator, at 5° to 10° C., for twenty-four hours. The main trunks of the coronary arteries were then dissected, and threads were placed on them for tying the cannulas used for injection. These were placed after the aorta, free from the pulmonary artery and surrounding tissue, had been opened by dividing it lengthwise down to its origin. The coronary system was washed out with warm (45° C.) saline, and then a radiopaque colored mixture was injected. The method of injection and the lead acetate, sodium diphosphate, and agar mixture were those recommended by Schlesinger.[1]

Roentgenograms were made of the anterior and lateral aspects of the heart; the viscus was then opened by Schlesinger's method of section and more roentgenograms made. A dissection of the minor branches, using the roentgenograms as guides, was then carried out.

For purposes of description the heart is considered as having an anterior and a posterior aspect, a left border (margo obtusus) and a right border (margo acutus), a base and an apex. The aortic cusps will be named according to their position: anterior right, anterior left, and posterior.

Altogether, thirty-one hearts have been studied, although some were only partially injected. They were obtained from dogs differing greatly in size, weight, age, and breed. For this reason, measurements are valid only for the individual observed and are given only for illustration.

DESCRIPTION

Authors describe two coronary arteries in the dog, the left and the right. Moore[2] found two right coronary arteries in 20 per cent of his animals. I have found constantly two left coronary arteries, the circumflex and the anterior descendens (*a. sulci longitudinalis anterioris*); in nearly one-third of the cases the septal artery also had an independent origin, and, more rarely, a fourth artery, which runs diagonally down the anterior aspect of the left ventricle, may be found. Usually only one right coronary artery was seen, but in some dogs there were two, and even three.

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Left Circumflex Coronary Artery.—This originates in a small fossa, or depression, in the aortic wall, situated, in 79 per cent of the animals, on a level with the edge of the anterior half of the anterior left aortic cusp, somewhat further back in the remaining 21 per cent. The diameter of the depression varies with the size of the dog, being about 4 mm. in a 20 kg. animal; its depth corresponds to the thickness of the aortic wall. The anterior descendens also originates in this fossa, to the right of the circumflex, but there is no common trunk as there is in man.

The circumflex artery runs in the left auriculoventricular sulcus; its first part is covered by the left auricular appendix; on reaching the sulcus longitudinalis posterior it descends along it toward the apex (*r. sulci longitudinalis posterioris*). In no case did the circumflex end before reaching the posterior longitudinal groove; this corresponds to Banghi and Crainicianu's type IV in man.

The length of the artery varies from 55 to 160 mm., depending on the size of the animal; its diameter near the aortic orifice varies from 1 to 2.5 mm.

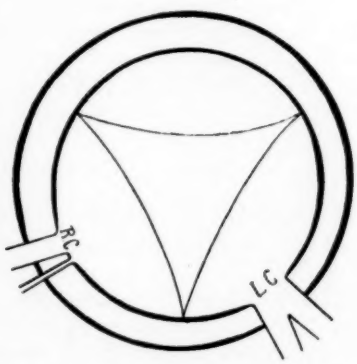

Fig. 1.—Origin of the coronary arteries in the aorta.

The *branches* of the circumflex can be distinguished as descending, or ventricular, and ascending, or auricular. There are two to six principal *ventricular branches,* and several minor ones. The most prominent are: (1) a branch leaving the circumflex at the level of the left border and descending toward the apex, usually ending 10 to 15 mm. before reaching it (*r. marginis obtusi*); (2) a branch arising shortly before the circumflex starts to descend, going to the posterior aspect of the right ventricle (*r. ventriculi dextri posterioris*); and (3) the terminal branch (*r. descendens posterior aut sulci longitudinalis posterioris*), which ends at the apex, or shortly before. Its length varies, depending on the size of the dog, from 25 to 85 mm.; it gives out branches to the posterior aspect of the left ventricle and the left papillary muscles. Shorter branches supply a narrow strip, about 10 mm. wide, of that part of the right ventricle contiguous to the posterior longitudinal groove, and several small branches penetrate the septum; but I have not

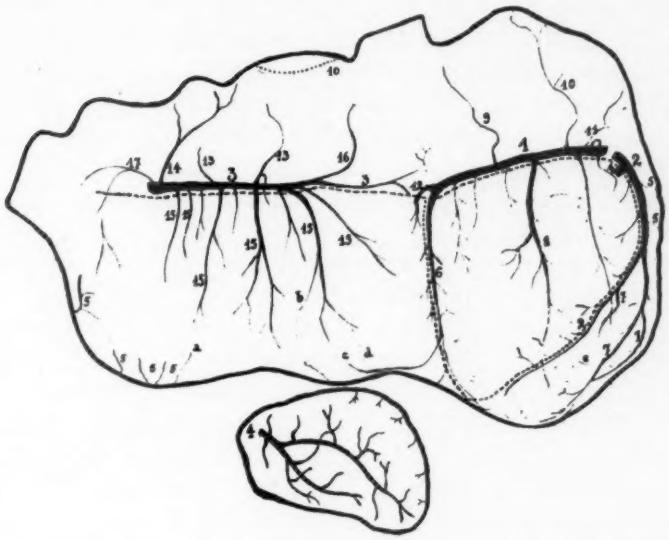

Fig. 2.—The coronary system of the dog: *1*, circumflex artery; *2*, a. descendens anterior; *3*, right coronary artery; *4*, a. septum ventriculorum; *5*, r. ventriculi dextri; *6*, r. sulci longitudinalis posterioris; *7*, r. ventriculi sinistri; *8*, r. marginis obtusi; *9*, *10*, and *11*, r. atrialis sinister; *12*, r. ventriculi dextri posterioris; *13* and *14*, r. atrialis dexter; *15*, r. ventriculi dextri; *16*, r. atrialis dexter posterior; *17*, r. adiposa; *a*, *b*, *c*, *d*, *e*, anastomoses.

Fig. 3.—The coronary system of the dog's heart injected, spread out, and radiographed according to Schlesinger's method.

found one which could be individualized as was that described by Bianchi and Spalteholtz (quoted by Condorelli[3]), irrigating, in some cases, the fibrous part of the septum. According to Haas and Kalm (quoted by Condorelli), this small artery nourishes the auriculoventricular node and the bundle of His, the branches of the bundle being supplied by the septal artery. Owing to its inconstancy, all of the auriculoventricular conduction system can receive its blood supply from the septal artery.

The ascending, or *auricular branches,* are two to four in number. Near the origin of the circumflex a branch is sent to the left auricular appendix, in some cases. In others it is given off by another branch of the circumflex, the *r. atrialis sinister anterior.* This nourishes the anterior and superior aspects of the left auricle, and, in 75 per cent of my cases, contributed to the supply of the sinoauricular node. In my series this branch never originated from the *a. descendens anterior,* as was noted by Condorelli. Other branches of the circumflex go to the posterior aspect of the auricle and the interauricular septum.

Anterior Descending Coronary Artery (a. descendens anterior, a. sulci longitudinalis anterioris).—This originates in the left coronary fossa to the right of the circumflex artery; it runs down the anterior longitudinal sulcus, ending, in some cases, a little (not more than 20 mm.) above the apex; in others it not only reaches the apex, but also goes up the posterior aspect a short way. Its length varies, depending on the size of the dog, from 60 to 110 mm., and its diameter near its origin varies from 1 to 2.5 mm.

The branches of this artery supply the anterior aspects of the left and right ventricles and the septum. The branches to the left ventricle are three to seven in number. One arises about 40 mm. from the origin of the artery; it is constantly found, and, because of its size, v. Schulthess-Rechberg (quoted by Condorelli) has named the site of its origin the "division of the anterior descending branch." In four of my thirty-one animals the first branch arose directly from the aorta in the left coronary fossa already described. It runs diagonally down the anterior aspect of the left ventricle, giving off small branches; it should be called *ramus ventriculi sinistri primus,* or, when originating in the aorta, *arteria ventriculi sinistri prima aut diagonalis.* Moore[2] describes this branch as originating from the circumflex.

The branches to the right ventricle number three to five; with the exception of the first one, they are all very small; they supply a narrow band, not more than 15 mm. wide, of the anterior aspect of the right ventricle, adjacent to the sulcus longitudinalis anterior.

The branches going to the septum are very small and short with the exception of the first one. This last originated, in 70 per cent of my animals, about 5 mm. from the source of the anterior descending artery, but in the other 30 per cent it arose directly from the left coronary

fossa. I have never seen it originate from the circumflex, as Baumgarten (quoted by Condorelli) has. Because of its constancy, importance, and not infrequently independent origin, it should be called *arteria septum ventriculorum*. This septal branch, or artery, penetrates the septum at its anterosuperior angle and ends in the posteroinferior angle. At first it lies superficially with respect to the right ventricular cavity, covered by only a few muscular strands. The second half penetrates deeply into the septum; it has numerous branches, of which the first, going upward, and the second, running downward, can always be individualized. This artery supplies the right papillary muscles and the whole septum, with the exception of the anteroinferior angle, which is nourished by the anterior descending artery, and the posterior border, which is irrigated by the terminal branch of the circumflex.

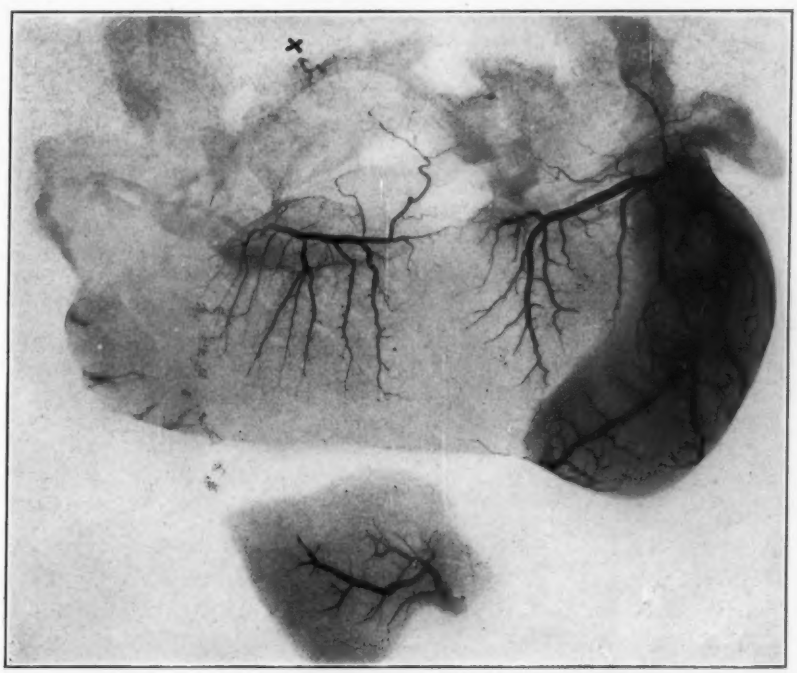

Fig. 4.—Coronary system of the dog; *x*, branch of the ramus atrialis sinister anterior irrigating the sinoauricular region (*10* in Fig. 2).

Right Coronary Artery.—This artery arises at the middle of the anterior right aortic cusp. In 40 per cent of my dogs there were two right coronary arteries, a principal and an accessory one. The latter, when it exists, is small and short; it usually originates in a small orifice at the anterior edge of the principal artery; less frequently it originates about 1 mm. in front of this ostium; it runs in a forward and downward direction, supplying a small portion of right ventricle below the origin of the pulmonary artery.

The principal right coronary artery lies in the right auriculoventricular groove in the midst of abundant fatty tissue; its first part is covered by the right auricular appendix. Ellemberger and Baum[4] and Condorelli[3] maintain that the right coronary artery does not pass the margo acutus in the dog; Ellemberger and Baum describe a *r. marginis acuti* as the terminal branch. Bianchi (quoted by Condorelli) also agrees that the right coronary supplies only the anterior and lateral aspects of the right ventricle. In my animals this artery always invaded the posterior aspect, ending about 5 mm. from the sulcus longitudinalis posterior. Its length varied between 30 and 65 mm., and its diameter between 1 and 1.5 mm.

The branches can be divided into descending, or ventricular, and ascending, or auricular. The ventricular branches number four to nine; none is especially remarkable for its size or constancy, and there is not even a constant *r. marginis acuti;* they supply the walls of the right ventricle, but nowhere do they reach its borders, which are nourished by other arteries.

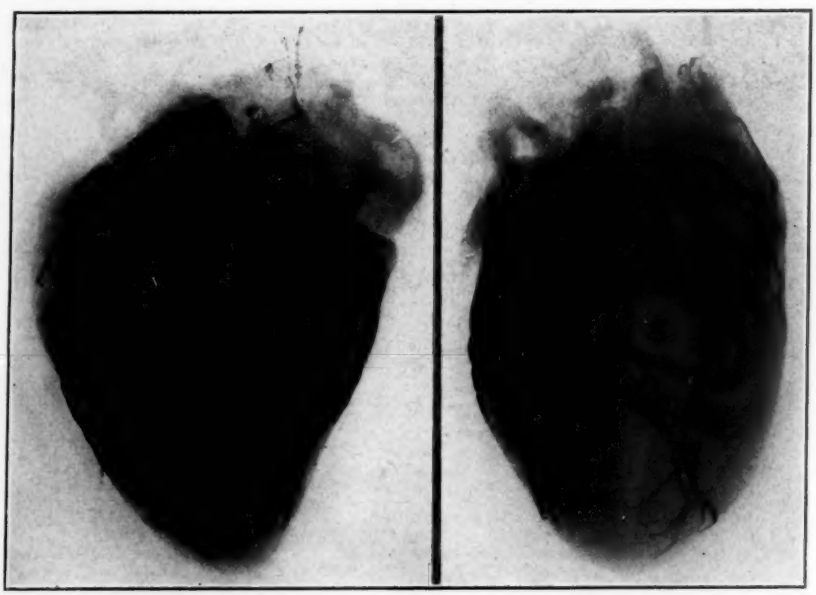

Fig. 5. Fig. 6.

Fig. 5.—Anterior aspect of the heart injected and radiographed.
Fig. 6.—Left aspect of the heart, injected and radiographed.

The auricular branches are three to five in number; they supply the right auricle. The first branch goes to the right auricular appendix. The most important is the *r. atrialis dexter posterior,* which irrigates the walls of the right auricle, the interauricular septum, and the sinoauricular node. This distribution coincides with that found by Maldo-

nado-Allende and Orías,[5] but differs from that described by Condorelli, who maintains that the S-A node is supplied by the *r. atrialis dexter anterior*. In this series the most important atrial branch of the right coronary artery originated near the end of the artery on the posterior aspect of the auricle, after the origin of an anterior branch and one or more of smaller caliber that could be denominated intermediate branches. It is, therefore, called *r. atrialis dexter posterior*, rather than *intermedius*, as it was designated by Meek, Keenan, and Theisen.[6] The territory irrigated by Meek, Keenan, and Theisen's *r. intermedius* is about the same as that supplied by the *r. posterior*, but the origin described is more proximal than that found in this series.

I have not been able to demonstrate the *a. adiposae* which Bianchi (loc. cit.) has found in all cases. As they arise very near the origin of the main arteries, I suppose they were not injected by the method I employed.

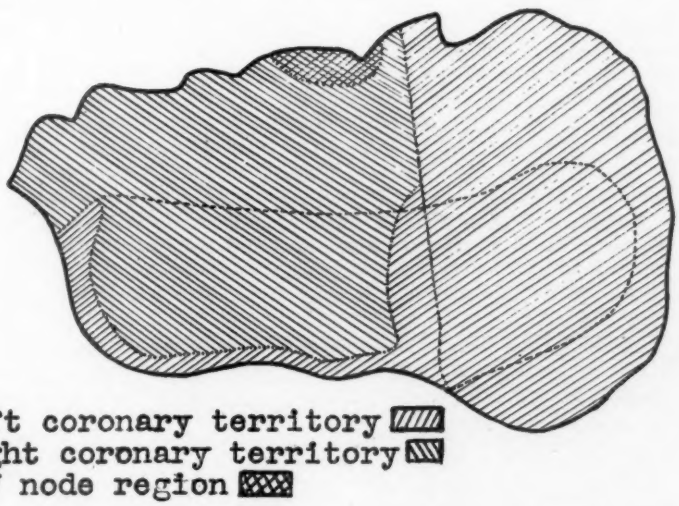

Fig. 7.—Left coronary territory, right coronary territory, and A–V node region supplied by right and left coronary arteries.

Anastomoses.—The existence of anastomoses can be shown when performing the saline injection; the fluid injected through a cannula placed in one artery flows out of the other arteries. Following Schlesinger's technique it is possible to locate these anastomoses by dissection. I have found fine connections between the ventricular branches of the right coronary artery and the right ventricular branches of the anterior descending artery and the terminal branches of the circumflex (*r. descendens posterior*). Also, I have seen anastomoses between the *r. marginis obtusi* and the left ventricular branches of the anterior descending artery. Communication is thus established between the territories of the three principal coronary arteries (right coronary, anterior descending, and circumflex). This by no means pretends to be a com-

plete list of all the anastomoses that exist; Baumgarten and Spalteholtz (quoted by Condorelli) maintain that they are very numerous.

Areas of Blood Supply.—As in other animals, but differing from man, in the dog the left coronary arteries supply a larger territory than the right coronary artery. The latter nourishes only the right auricle, the interauricular septum, and the middle parts of the right ventricle. The circumflex coronary artery supplies the left auricle, the lateral and posterior aspects of the left ventricle, the posterior edge of the interventricular septum, and a narrow strip of the posterior aspect of the right ventricle. The anterior descending coronary artery supplies the anterior aspect of the left ventricle, that part of the anterior aspect of the right ventricle adjacent to the anterior longitudinal groove and the apex, and the interventricular septum. The sinoauricular node receives its blood supply from the right coronary artery and (75 per cent of my observations) also from the *r. atrialis anterior* of the circumflex.

I wish to thank Professor J. T. Lewis for the help and encouragement he has given me in the preparation of this paper.

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HYPERTONIC GLUCOSE SOLUTION IN ANGINA PECTORIS

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SINCE glucose is a fundamental nutritive substance for all tissues and organs of the body, it has found very extensive use in medicine. Recently several investigators observed that the isolated heart, when perfused with glucose, responded with stronger contractions. Hence, its clinical use seemed logical.

One of the effects of concentrated glucose solution was thought to be vasodilatation. It seemed very probable that this action could be beneficial to the patient with heart disease, especially with angina pectoris. Hence, concentrated glucose solution became widely popularized in the treatment of angina pectoris. We employed this therapy for more than 30 patients with typical effort angina. The results when critically and carefully followed were never good, and it was noted that several patients developed anginal attacks immediately after the injection of concentrated glucose solution. Severe precordial pain, extreme anxiety, and profuse perspiration were noted, and nitroglycerine was necessary for relief. Other physicians whom we questioned in regard to this matter confirmed our observations, and it was therefore deemed advisable to investigate the effect of hypertonic glucose on the electrocardiogram.

We studied (1) the effect of hypertonic glucose solution, injected intravenously, on the electrocardiogram of patients with effort angina; and (2) the effect of hypertonic glucose solution on the after-exercise electrocardiogram of patients who had cardiac pain on effort.

In a previous paper,[1] we reported the electrocardiographic changes after injecting hypertonic glucose solution in patients with normal hearts and in patients with heart disease but without effort angina. In most instances there was a slight increase in the height of the positive T waves after the injection of hypertonic glucose solution in the patients with normal hearts. However, in a group of fifteen patients with heart disease, but without effort angina, quite different results were obtained. In eight of these cases, in which coronary sclerosis existed, the electrocardiographic changes noted were flattening of an upright T wave or an increase in the depth of an already inverted T wave, and increased depression or elevation of the S-T segment. The patients with rheumatic heart disease in this group presented no electrocardiographic alterations.

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I. ELECTROCARDIOGRAPHIC CHANGES AFTER THE INTRAVENOUS INJECTION OF HYPERTONIC GLUCOSE SOLUTION IN PATIENTS WITH ANGINA OF EFFORT

In this group there were fifteen patients, all of whom gave a history of typical cardiac pain on effort. Twelve of the patients had arteriosclerotic heart disease, three of whom also had hypertension, one patient had syphilitic heart disease with insufficiency of the aortic valve, one patient had rheumatic aortic stenosis, and one patient had rheumatic mitral stenosis. In each instance an electrocardiogram was taken first with the patient at complete rest, and then electrocardiograms were taken immediately, five minutes, and, in several instances, ten minutes after the intravenous injection of 50 c.c. of 50 per cent glucose solution. Twelve of the fifteen patients showed marked electrocardiographic changes following the injection of the glucose. Seven of these patients developed some degree of precordial pain, and in two the pain was so severe that nitroglycerine had to be given. The pain in these two instances was associated with marked pallor and profuse perspiration and lasted ten minutes; the nitroglycerine gave prompt relief.

The changes observed were similar to those seen in patients with coronary sclerosis without effort angina but were frequently much more pronounced. In two instances there was a definite increase in heart rate associated with the pain, but this was probably a consequence rather than a cause of the pain, in view of the fact that angina after the injection of glucose was observed without any change in rate. In one case we noted that the heart rate increased only *after* the appearance of precordial pain.

Fig. 1 shows the electrocardiograms of a 54-year-old woman with a history of angina on slight effort and following the ingestion of a heavy meal. Hypertension was also present. The three limb leads are here recorded with the patient at rest (Fig. 1*a*), and it will be noted that auricular fibrillation and a slight depression of the S-T segments in Leads I and II are present; the latter was due to digitalis. The T waves are upright in all three leads. The beating is irregular, and the rate is 70 per minute. Tracings were taken immediately after 50 c.c. of 50 per cent glucose solution had been given intravenously (Fig. 1*b*). The patient complained of precordial pain immediately after the injection. The S-T segments in all leads are depressed; this is particularly evident in Lead II. T_3 is now inverted, and the rate is 110 per minute. Tracings were then taken 5 minutes after the injection (Fig. 1*c*), and it will be noted that the changes are similar to those in Fig. 1*b*, but less pronounced. The original pattern is evidently returning. The pain was not quite as intense, and the rate diminished to 100 per minute.

The patient had a recurrence of very severe pain about 7 minutes after the injection and broke out into a cold sweat. The next trac-

ings were taken 10 minutes after the initial injection (Fig. 1*d*), and it will be noted that the S-T segments are now more depressed than in Fig. 1*c*. Coincident with the return of pain, it will be noted that the rate increased to 120 per minute.

The same results were obtained when the injection of hypertonic glucose solution was repeated.

Fig. 2 shows the electrocardiograms of a 55-year-old woman with a history of precordial pain of several years' duration, precipitated, as a rule, by effort. Fig. 2*a* was taken with the patient at rest. There is slight depression of the S-T segments in Leads I and II. The cardiac rate is 108 per minute. The next tracing was taken immediately after giving the glucose (Fig. 2*b*). Only 20 c.c. of the solution were given because the needle slipped out of the vein. Note the greater depression of the S-T segment in Lead II, and the appearance of slight displacement in Lead III. At this time the patient complained of slight substernal pain. The rate was 110 per minute.

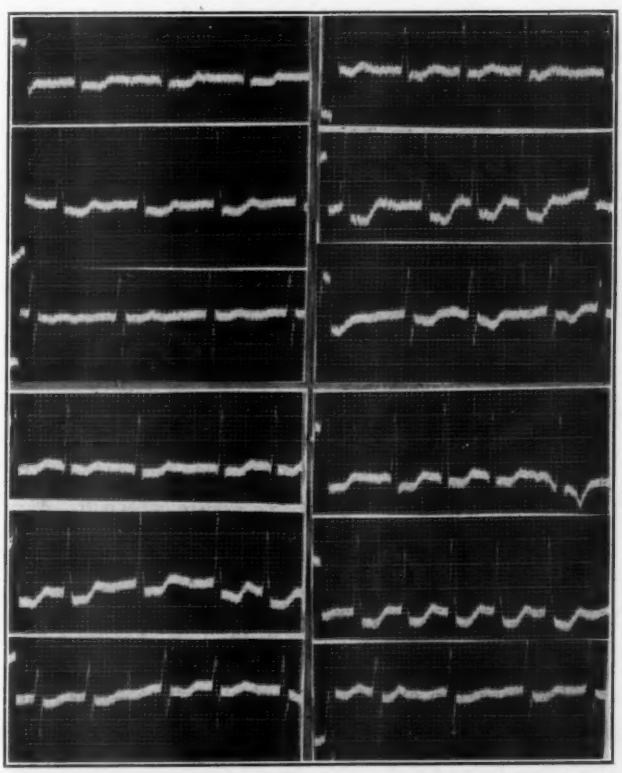
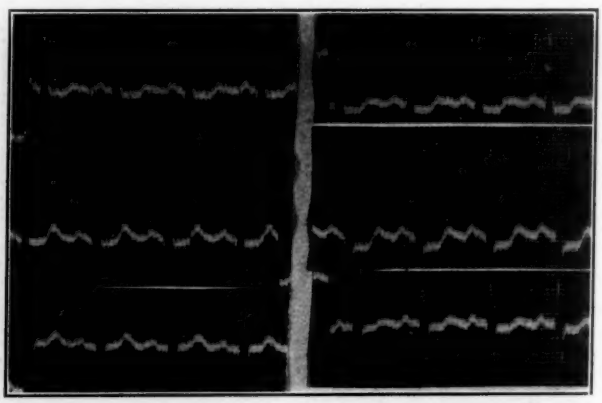


Fig. 1.—Electrocardiograms of a patient, with angina of effort: *a*, before glucose injection; *b*, immediately after glucose injection; *c*, 5 minutes, and *d*, 10 minutes, after glucose injection.

The electrocardiograms in Fig. 3 are those of a 32-year-old woman with a 4-year history of known rheumatic mitral stenosis. She also complained of frequent attacks of precordial pain. The four leads with

the patient at rest are reproduced in Fig. 3*a*. They reveal no abnormality other than a slight diminution of voltage below the normal limits. The cardiac rate at this time was 60 per minute. Hypertonic glucose (50 c.c. of a 50 per cent solution) was then injected intravenously, and electrocardiographic tracings were taken immediately thereafter (Fig. 3*b*). It will be noted that the high, positive T waves in Leads I and II have disappeared. T_1 is now invisible, and in Lead II there is even slight negativity of the T wave. Slight depression of the S-T segment in Lead II is also present. The high, positive T wave in the chest lead (left arm wire to precordial electrode) is changed to a bifid T with a deep, inverted peak. Slight increase in rate, namely, to 75 per minute, and slight substernal discomfort were present. The next tracings were taken 5 minutes after the injection (Fig. 3c), and the changes are practically the same as in Fig. 3*b*, although not quite so marked. It will be noted that the rate in Fig. 3*c* is the same as in Fig. 3*a*, and yet pronounced changes are present.



a. *b.*

Fig. 2.—This patient also had effort angina. *a*, Before glucose injection; *b*, immediately after the injection of hypertonic glucose solution.

II. THE EFFECT ON THE AFTER-EXERCISE ELECTROCARDIOGRAM OF INJECTING HYPERTONIC GLUCOSE SOLUTION

It was pointed out by one of us, in a series of investigations,[2, 3] that registration of the electrocardiogram after exercise can render considerable help in the diagnosis of coronary artery disease. In patients who complain of angina on effort there is usually stenosis of a coronary artery, either because of sclerosis of the vessel or syphilitic narrowing of its ostium. When these patients are at rest the blood supply to the heart can be sufficient despite the stenosis, pain is absent, and the electrocardiogram may be normal. After exercise, which is graded according to the condition of the patient and never excedes the amount that the patient engages in many times during the course of the day of his own accord, the blood supply to the heart becomes insufficient, and the

electrocardiogram presents marked changes. Pain can, but need not, appear. If the same patient exercises immediately after taking nitroglycerine, these electrocardiographic changes do not present themselves. Other vasodilators, injected intravenously, can also prevent these electrocardiographic changes or diminish the degree of the changes.

One would expect that the after-exercise electrocardiogram, taken immediately after the injection of hypertonic glucose solution in patients with coronary stenosis, would show less change if glucose has a definitely dilating effect on the coronary arteries.

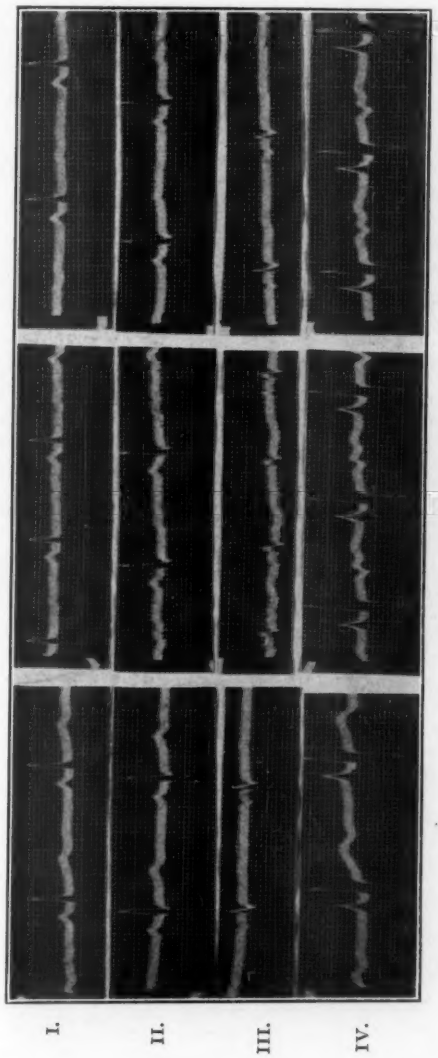


Fig. 3.—Electrocardiograms of a patient with mitral stenosis and attacks of precordial pain. *a*, Before glucose injection; *b*, immediately, and *c*, 5 minutes, after the injection of glucose.

This investigation was carried out in seventeen cases. All patients had angina of effort and either coronary sclerosis or syphilitic aortitis. The attacks were typical, and nitrites worked promptly in all. Under

constant conditions, an exercise test was carried out first in all cases. The electrocardiogram was recorded before the exercise and immediately after, as well as 2, 5 and, oftentimes, 10 minutes afterward. Several repetitions showed that the exercise reaction was always the same. Forty cubic centimeters of a 40 per cent glucose solution were then given intravenously, and, 5 minutes later, after the same amount of work, electrocardiograms were taken in the same fashion.

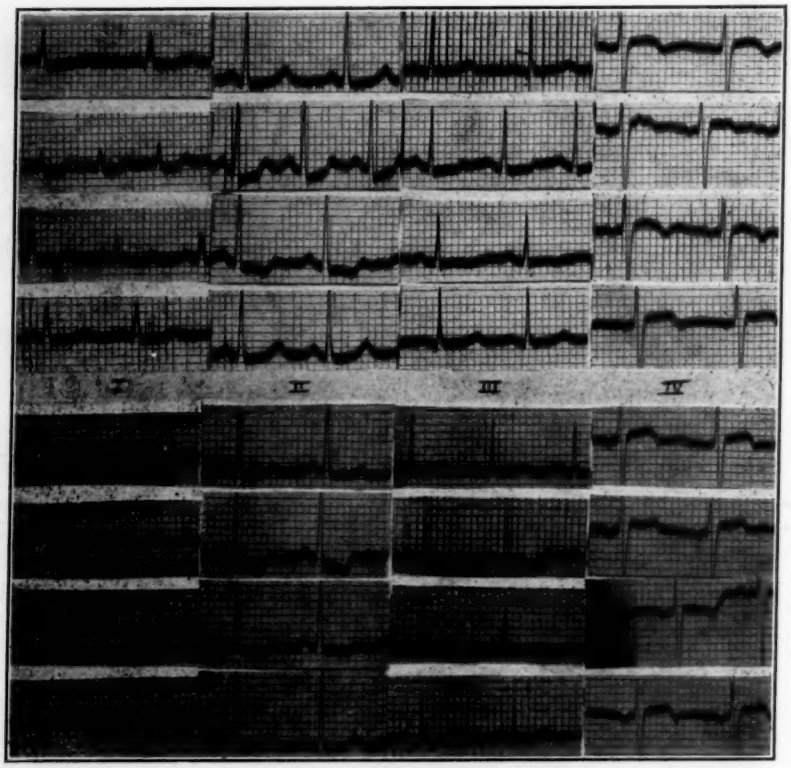


Fig. 4*A*.—Electrocardiograms of a patient with aortic insufficiency. Before exercise (top row), and following exercise (lower 3 rows).

Fig. 4*B*.—Same patient as 4*A*. Electrocardiogram 5 minutes after injection of glucose with the patient at rest (top row), and after exercise (lower 3 rows).

In twelve of the seventeen cases, the electrocardiogram showed pathologic alterations after exercise, namely, depression of the S-T segments and abnormal T waves. In two cases the results were questionable, and in three cases the electrocardiograms after effort showed only the familiar physiologic changes. After the injection of glucose, the alterations in the electrocardiogram after exercise were unquestionably accentuated, and they occurred in all cases. In seven cases the reaction to exercise after the injection was worse than before. Never was the reaction less pronounced. These results are illustrated in Figs. 4 and 5.

Fig. 4 is from a 34-year-old patient with insufficiency of the aortic valve, the etiology of which could not be established with certainty; it was probably syphilitic. The patient suffered severe anginal attacks which were promptly relieved by nitroglycerine. The after-exercise electrocardiogram, which was recorded many times, became immediately positive, and showed the same changes that occurred in spontaneous attacks while at rest during a hypertensive crisis.

In Fig. 4*a* we see the three limb leads and chest leads (left leg wire to the area of absolute heart dullness to the left of the sternum) next to each other. The uppermost row of curves shows the resting electrocardiogram, in which the only item of note is the low T wave in Lead I. No significant changes are present. Two minutes after the exercise test (second row), there appears a definite depression of the S-T segment in Lead I, the T waves in Leads II and III are deeply negative, and in the chest lead the slightly negative T after the elevated S-T segment is changed to a positive T. After 5 minutes (third series), the changes are less marked. After 10 minutes (lowest series), the original pattern has returned. The time necessary for the changes to disappear varied from patient to patient; in some cases it was from 20 to 40 minutes.

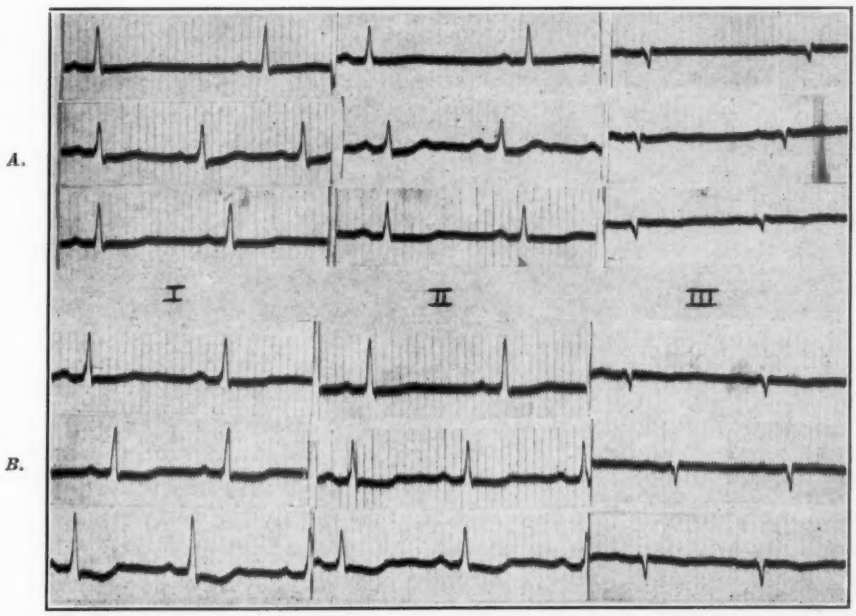


Fig. 5*A*.—This patient had coronary sclerosis with angina of effort. The first row before exercise, and the next 2 rows after exercise.

Fig. 5*B*.—Same patient as 5*A*. First row electrocardiogram before exercise, 5 minutes after injection of glucose. Second and third rows, after exercise.

Fig. 4*b* shows the results of an exercise test 5 minutes after the injection of 40 c.c. of 40 per cent glucose solution. The resting electrocardiogram has the same appearance as that in Fig. 4*a*. The same

changes appear after the exercise as in the previous experiment, and the time necessary for them to disappear is also the same. Upon repeating the experiment several days later, the results were identical.

Fig. 5 is from a 63-year-old patient with coronary sclerosis and angina of effort. The T wave is absent in Lead I and is hardly visible in Lead II. Immediately after the exercise test, high, normal T waves appeared (not illustrated). This is a normal exercise reaction and depends upon increased sympathetic tonus. After 2 minutes (second series), a definite depression of the S-T segment appeared. However, this does not exceed normal limits, and the T waves are more nearly normal than they were before the exercise. Five minutes after the exercise test we see in the lowest series a definite depression of the S-T segments, this time in all leads and unquestionably of abnormal degree.

On the next day, 2 minutes after exercise, and 5 minutes after the injection of hypertonic glucose solution (Fig. 5*b*), the depression of the S-T segment was more marked than in Fig. 5*a*, and the height of the T wave was less. Five minutes after exercise (lowest series), an even more marked change than in Fig. 5*a* appeared. The pain reaction after exercise was greater than on the previous day, when glucose had not been injected.

DISCUSSION

Several theories have been advanced to explain the beneficial effects of glucose upon the heart. The following, especially, require consideration:

1. There is improvement of the nutrition of the heart by direct action of the glucose on the muscle fibers.

2. Dilatation of the coronary arteries is brought about by direct alteration of the physical properties of the cells.

3. An increase of the coronary blood flow is produced by other indirect mechanisms.

1.—It has long been assumed that one of the reasons for failure of the heart was that its nutritive supply, especially its store of carbohydrate, was diminished. In animal experiments it has been shown that glucose is necessary for cardiac efficiency.[4] Although adequate proof was lacking, it was easy to infer that the failing heart might be deprived of, or could not utilize, combustible carbohydrate.

It has been frequently recommended that carbohydrate be given by mouth in the treatment of patients with heart disease,[5-9] in order to improve the nutrition of the heart. For the past twenty years glucose has also been used intravenously with many favorable results. It has been recommended in amounts varying from 20 to 200 c.c. and in concentrations ranging from 20 to 50 per cent.[10, 11]

However, despite the many reports favoring the use of glucose to improve cardiac nutrition, it has certainly not been proved that glu-

cose actually accomplishes this. The improved efficiency noted in the heart-lung preparation of Bayliss and co-workers[4] does not necessarily mean that the human heart will respond in the same way, since one cannot apply too fully results obtained on the heart of the experimental animal under unnatural conditions to the heart of the human subject. The problem of the effect of hypertonic glucose on the heart seems to be more intimately related to coronary blood flow.

2.—A widely accepted theory of the action of hypertonic glucose assumes a direct effect upon the vessel wall. The physical properties of the muscle cells in the walls of the coronary arteries are supposed to be altered by virtue of osmotic and colloidoclastic effects.[12, 13] The colloidoclastic effect is presumed to cause a temporary change in the quality of the blood and tissue colloids. In this way, or through osmotic effects, a dilatation of the coronary arteries should take place.

In animal experiments, using the Morawitz cannula, Salomon[13] employed a 20 per cent glucose solution and reported a direct dilating effect upon the coronary arteries. He observed this phenomenon in thirty-seven out of forty-four animals. For clinical use he advocated more concentrated solutions.

3.—Ginsberg, Stoland, and Loy[14] found that in the intact animal (dog) 10 c.c. of a 50 per cent dextrose solution increased the coronary circulation from 10 to 100 per cent, or more, and that the increased rate of flow was maintained for 40 minutes, or more. The increase occurred in the absence of tachycardia and without a rise in blood pressure, and it was independent of neurogenic mechanisms. Hypertonic saline solution did not produce as marked an increase of flow as hypertonic glucose solution. The height of the blood sugar was unrelated to the amount of coronary blood flow. In six heart-lung preparations these authors failed to observe vasodilatation and hence concluded that glucose does not have a direct effect upon the vessel wall. Hydremia was probably the most important factor in increasing the coronary blood flow, despite the fact that the specific gravity and viscosity of the blood quickly returned to normal, while the augmented flow through the coronary vessels continued.

Frey and Hess[15] performed a series of experiments similar to those of Ginsberg, et al., but they used the "thermostromuhr" to measure the coronary blood flow. They employed 10 c.c. of a 50 per cent glucose solution and noted that, in some animals, they obtained a rapid, marked dilatation of the coronary vessels. In other animals, however, they observed only a slight dilatation, while in still other instances, a diminution of blood flow occurred. In 61 per cent of the cases an augmentation of blood flow occurred, whereas in 26 per cent of the cases an actual diminution of flow was observed. The blood pressure remained unchanged after the introduction of the glucose. These

authors discuss the possibility that glucose acts on the adrenalin-insulin mechanism and, in this way, produces alterations of the flow of blood through the coronary arteries.

It has long been known that hypertonic glucose solution exerts a marked osmotic effect when introduced into the blood stream.[16-19] In the presence of normally functioning coronary vessels, the plethora produced by the injection of hypertonic glucose solution may contribute to the increased blood flow. Changes in blood pressure and cardiac rate cannot play a role, since, as has been pointed out by several authors, the pressure and rate are unaffected by the injection of hypertonic glucose solution. It is important to correlate these facts, as will be pointed out later.

Little need be said regarding the possible dilating effect of glucose upon the smaller coronary vessels. It has been suggested that glucose can dilate coronary vessels, like some known vasodilators, by vagal inhibition or sympathetic stimulation. The action of glucose, however, is entirely independent of nerve supply.[14]

From an extensive review of the literature, Martin[20] concludes that hypertonic glucose solution, given intravenously, improves the coronary blood flow and increases the venous return and cardiac output.

Judging from the foregoing remarks, there would seem to be a definite rationale for the use of hypertonic glucose solution in the treatment of those forms of heart disease associated with diminution in coronary blood flow. Many observers have reported that favorable results in the treatment of angina pectoris and congestive heart failure were obtained by using hypertonic glucose solution in varying amounts and concentrations.[21-25] Some authors advised the use of insulin with the hypertonic glucose solution.[11] Critical appraisal, however, of the literature does not warrant too optimistic an opinion with regard to the belief that hypertonic glucose solution is beneficial in coronary artery disease. Scattered through many reports one finds evidence that precordial pain occasionally developed during treatment,[24-26] and the objective results often do not warrant the conclusions drawn.

There is a question whether or not T-wave alterations always indicate myocardial damage.[27] A positive T wave may actually be increased in height in the presence of a definite myocardial lesion, and it has not been proved that in every instance an inverted T wave means myocardial injury. Of much greater importance, however, is the association of cardiac pain with inversion of the T waves after the glucose injection. This must invariably mean myocardial impairment, since seven patients developed precordial pain. Hence, glucose in hypertonic concentration is harmful and alters the ratio of blood supply to the oxygen demand of the myocardium. This statement is

also borne out by the fact that seven of seventeen patients with effort angina developed more intense pain after exercise when hypertonic glucose solution had been given previously.

In practically all of our cases in which there was reason to believe that the coronary arteries were sclerosed, definitely abnormal changes appeared in the electrocardiogram, but, as previously reported,[1] in the cases of rheumatic valvular lesions, and in patients with hypertension whose coronary arteries were probably intact and patent, no electrocardiographic changes were noted.

In one case of mitral stenosis in which there was precordial pain, marked changes in the T wave were observed (Fig. 3*b*) after the injection of hypertonic glucose solution. During an attack of anginal pain, patients with mitral stenosis frequently have abnormal electrocardiograms.[3] There is reason to believe that, since cardiac hypertrophy exists, and the stroke volume is small, myocardial ischemia results when the work of the heart is increased without a proportionate augmentation of the coronary blood flow. Patients with severe rheumatic involvement of the aortic valve may, however, show no changes. In one case of rheumatic stenosis of the aortic valve no alteration of the electrocardiogram occurred after the injection of hypertonic glucose solution, and yet this patient had severe effort angina. At autopsy, stenosis of the aortic valve was found, but the coronary vessels were entirely free of sclerosis.

It is apparently true that glucose dilates the coronary vessels in experimental animals, although contradictory findings have been reported,[15] but an increased blood flow to an organ does not necessarily indicate increased oxygenation. An increased velocity of blood flow may diminish the utilization of oxygen, for, because of the rapid transit of blood through the smaller vessels, oxygen cannot be removed quickly enough by the tissues. When total blood flow is increased, the capillary flow is often not comparably augmented because of short circuiting. Frequently, in cases of arteriosclerosis obliterans of the lower extremities, if the venous channels are tapped the blood will be found to be well oxygenated, indicating failure of oxygen utilization. Moreover, sclerotic vessels may fail to show the same dilatation as the healthy vessels of the experimental animal. Under such conditions anoxia results, since the blood volume is increased, the stroke volume is greater after the intravenous injection of glucose, and the oxygen requirement becomes greater without a comparable increase in coronary blood flow.

It was found[28] that after the intra-arterial injection of hypertonic salt solution there was a diminished oxygen utilization in the tissues. This phenomenon was believed to be caused by a change in the vessel wall between tissue and blood which prevented the oxygen from being given up. This explanation may be applicable to the action of hypertonic glucose solution on the coronary circulation, for, despite increased

blood flow brought about by intravenously injected hypertonic solutions, the oxygen supply to the tissue may actually be diminished because of failure of utilization.

Although an increased cardiac rate was observed in some of our patients, this could not play a role in the production of pain after the injection of glucose, since we have observed the same electrocardiographic changes without any change in rate whatsoever. We are inclined to believe that any increase in cardiac rate was the result, rather than the cause, of the pain.

One of the possible explanations for the cardiac pain which deserves consideration is that the glucose may have stimulated the secretion of insulin. Insulin has been shown to produce changes in the T wave[29] and may even precipitate cardiac pain. Glucose is one of the best agents for stimulating the production of insulin and has been called the insulin hormone.[30*] Curves have been plotted to show that hypertonic glucose solution stimulates the production of insulin.[31] This being the case, it would seem possible that the cardiac pain which the patients developed after the injection of hypertonic glucose solution was an insulin effect.

There are certain observations which indicate that insulin has no direct action on the coronary vessels. In the first place, there is no parallelism between the height of the blood sugar and any electrocardiographic alterations. Marked electrocardiographic changes have been observed before hypoglycemic levels were reached. In the second place, there are many observations which prove that the hyperadrenalinemia accompanying the fall of blood sugar produces the changes. Even if insulin has a direct action on the coronary vessels it is probably secreted in too small an amount to cause spasm.

Investigations are now under way to determine whether hypertonic saline and hypertonic sucrose solutions can produce the same changes as hypertonic glucose solution. It is necessary to ascertain whether the results with glucose are specific, i.e., whether the results depend upon the concentration or the nature of the injected substance.

In conclusion, we wish to point out that the beneficial effects of intravenously injected hypertonic glucose solution upon the heart are very questionable. That it has a marked osmotic effect in pulmonary edema, cerebral edema, and in cases of increased intraspinal pressure cannot be denied, but it is questionable whether or not hypertonic glucose solution has any place in the treatment of coronary artery disease. It has been shown to cause severe angina and, therefore, may be deleterious. It should be used cautiously in patients with coronary sclerosis, and if it is to be used at all (pulmonary edema), we recommend that it be used in conjunction with vasodilators, such as nitroglycerine.

*This has also been denied.[32]

SUMMARY

In two series of cases we studied the effect on the heart of the intravenous injection of hypertonic glucose solution. In Group I it was observed that in patients with effort angina and coronary arteriosclerosis the injection of hypertonic glucose solution produced marked electrocardiographic changes and frequently caused pain. In Group II it was observed that patients with effort angina and pathologic alterations of the electrocardiogram after exercise developed the same, and even more marked, alterations of the electrocardiogram when hypertonic glucose solution was given shortly before the performance of the exercise test.

The various theories concerning the effect of hypertonic glucose solution on the blood and coronary arteries were discussed, and the possible causes for the production of cardiac pain after the injection of hypertonic glucose solution were reviewed.

Since the submission of this paper for publication there has appeared, in the May, 1939, issue of this JOURNAL, an article by L. B. Ellis and J. M. Faulkner on the circulatory effects of 50 per cent dextrose and sucrose solutions on patients with heart disease. The authors cautioned that the increase of plasma volume which attends the injection throws an extra load on the circulation similar to that caused by the injection of large amounts of fluid in patients whose circulatory balance is already precarious.

We wish to express appreciation to Miss Mover and Miss Pringle for technical assistance.

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DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

1. Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans

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INTEREST in the therapeutic use of various tissue extracts was stimulated by the work of Frey and Kraut (1926), who prepared and studied a pancreatic extract, kallekrein (later called padutin). It was reported to inhibit the crural pain causing intermittent claudication. Wolffe, Findlay, and Dessen (1931)[2, 3] described extracts of pancreatic tissue which gave therapeutically similar results. Schwarzmann (1930)[4] reported improvement following the use of skeletal-muscle extract in three patients with intermittent claudication. Nuzum and Elliot (1931)[5] were unable to demonstrate vasodilatation in animals after intramuscular or subcutaneous injection of kallekrein. Barker, Brown, and Roth (1935)[6] found intermittent claudication present in 90 per cent of their patients with peripheral arterial disease. They noted a definite lessening of this symptom following the use of a pancreatic tissue extract. One of the present authors[7] reported similar results from our clinic in 1935. The substances used in the above studies produced pain and sometimes redness and swelling at the site of injection. Mild systemic reactions, including slight chilliness and fever, occasionally occurred.

DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

Following suggestions made by members of this clinic, and others, the Sharp and Dohme Laboratories undertook to refine and fractionate extract #568. Deproteinated pancreatic extract represents one of these fractions.

It is a colorless, saline solution of a chemically purified, protein-free, nitrogenous fraction, derived from an acid-alcohol extract of beef pancreas. Physiologic tests show that it is free from insulin, histamine, and acetylcholine. It contains approximately 2.5 per cent of solids, including 0.25 per cent of nonprotein nitrogen, 0.9 per cent of sodium chloride, and 0.25 per cent of phenol as a preservative. It is adjusted to a pH of 6.5 to 6.8.

It is assayed by comparing its effect with that of a standard preparation on the arterial blood pressure of anesthetized dogs. This standard preparation is of such potency that 1 c.c., in a large series of dogs, gives an average lowering of arterial blood pressure equivalent to the rise in arterial blood pressure produced by 0.01 mg.

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of epinephrine in the same dogs. The standard is preserved by the lyophile process, and stored in the dried state at 5° C. Each new lot of deproteinated pancreatic extract is standardized by comparing its depressor effect with that of a solution of the standard preparation on the normal and atropinized dog. The physiologic action of each lot is also studied by means of the heart-blocking effect in mice. Two cubic centimeters of depropanex are injected into white, female mice, and an electrocardiograph is used to ascertain whether heart block occurs. The material is injected intraperitoneally and should not cause death from heart block in any of at least three mice within fifteen minutes. Its depressor action in urethanized rabbits is also noted.

INTERMITTENT CLAUDICATION

The term intermittent claudication, as used in this report, may be defined as limping due to a pain or cramplike sensation, or as a sense of extreme fatigue most commonly localized in the calf, thigh, or foot muscles, induced by a limited amount of walking or other leg effort. This may be so severe as to prevent continued action of the group of muscles involved. A similar phenomenon may occur in other muscle groups under unusual conditions. Muscle spasm or muscle failure severe enough to cause the subject to fall may occur if exercise is continued. The pain or disagreeable sensation is usually relieved within a few minutes by cessation of muscular effort, frequently without change in position. The symptoms are not considered typical if they occur during rest. The amount of muscular effort necessary to produce this syndrome is fairly constant in most individuals during any one phase of the disease which causes it. Weather, environmental temperature conditions, and complicating illnesses may bring about some fluctuation in this regard. For more than five years we have been studying the effects of various pancreatic and heart-tissue extracts on this syndrome, and during the past year we have used deproteinated pancreatic extract in these studies.

METHOD

A. *Apparatus.*—In order to evaluate the effects of these extracts, we have found it essential to use a method of measuring the amount of work per unit of time necessary to produce this syndrome. Certain previous workers[6] depended on measuring timed walking. Landis, et al.,[8] used an ergometer, the muscle contractions being rhythmically induced by a faradic current applied to the leg. Berry,* at our clinic, devised a vertical stand fitted with a foot pedal which, when depressed, raises a weight of 13.6 pounds (Fig. 1). The patient stands upright on this apparatus in the same position in which he normally walks, with the foot of the extremity to be tested on the pedal. The other foot is placed on an adjoining platform. He grasps the upper bar with his hands to maintain his balance. The entire foot is kept on the pedal, and as the anterior portion of the foot is depressed to lift the weight the muscles of the leg used in walking are brought into play. The patient is paced at 120 steps per minute with a stop watch or metronome, and he is not allowed to stop until the pain, cramp, or fatigue in the calf or thigh becomes so severe that he is unable to continue.

*Dr. Maxwell Berry, now Fellow, Mayo Clinic, Rochester, Minn.

This method of measuring claudication time quite satisfactorily maintains, as a constant, the work done per minute by the muscles being tested. Care must be exercised that other sets of muscles are not thrown into action when the fatigue syndrome begins. This can be practically prevented by having the patient maintain an unchanged position on the apparatus. The room temperature should be kept constant. In our experiments, a temperature of 20° ± 1° C. was used. This test is convenient in that it takes a relatively short time to produce the syndrome.

B. *Procedure.*—The patient rested by sitting for one-half hour after reporting to the examiner. The first control test was performed, and, following another rest of one-half hour's duration, a second control test was made. The times for these two tests were in most instances very nearly identical. Three cubic centimeters of the extract to be tested were injected intramuscularly after the second test. One-half hour later a third test was made.

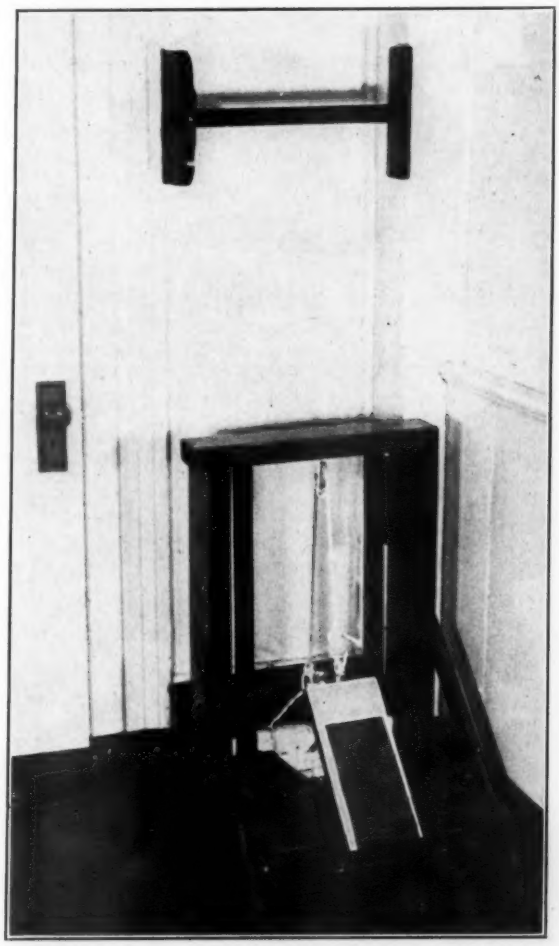

Fig. 1.

Using the above technique, the effect of deproteinated pancreatic extract was determined in twenty-seven patients with definite arteriosclerotic disease of the vessels of the lower extremities. Each patient was carefully studied by means of

oscillometric readings, roentgenograms, arteriograms, and other procedures, as indicated. They were all ambulatory. None had gangrenous lesions. After the original tests, the treatment consisted of 3 c.c. of the deproteinated pancreatic extract intramuscularly triweekly. The tests were rechecked frequently. Patients have now been followed as long as nine months. During the course of treatment each patient received, on one or more occasions, without his or her knowledge, 3 c.c. of physiologic salt solution as a control. An identical test was performed one-half hour after the saline was given. As stated above, deproteinated pancreatic extract is colorless, and, when injected intramuscularly, it causes no more pain than saline.

The ages of the patients varied from 50 to 80 years, the average being 62 years. There were twenty-four males and three females. All were white. Ten were Hebrew. Thirteen had received no previous treatment for their vascular disease. Fourteen had received previous treatment, such as other tissue extracts, suction-pressure, or intermittent venous occlusion. Such treatment was discontinued before the original tests with the pancreatic extract now being studied were made. All of the patients were advised not to use tobacco, and were instructed to take warm foot baths nightly, wear warm socks and proper shoes, and take proper care of the nails and corns.

RESULTS

The tables (Nos. I, II, and III) show the results obtained. Table I lists eight patients with untreated, uncomplicated, arteriosclerotic vascular disease. Six showed improvement, and two, no improvement, with the initial tests. All of those receiving ten or more treatments were benefited.

Table II lists five patients, untreated, but with complicating diabetes, heart disease, varicose veins, or other abnormalities which might have had a relationship to this condition Four showed improvement, and one, no improvement, with the initial tests. The four were improved after ten or more treatments. The one patient who was not benefited by the initial dose was not treated.

Table II lists fourteen patients who had been treated previously by other means, and includes patients both with and without complicating diseases. Thirteen of these showed improvement after the initial test. In one instance (14) the benefit was so slight as to be inconsequential. Ten individuals received ten or more treatments, and all of these showed improvement.

The saline which was used as a control produced results of no significance in these series.

Table IV summarizes the first three tables. The initial claudication time varied from an average of 1′ 26″ to 1′ 43″ in these groups, with extremes of 35″ and 2′ 30″. All tests were discontinued if claudication had not developed within 5 minutes. The actual averages are, therefore, greater than the averages given whenever so indicated in this table. One-half hour after the initial 3 c.c. of deproteinated pancreatic extract, the average claudication time for all patients was greater than 3′ 1″, an increase of about 100 per cent. This gain was

temporary with the first few injections. Nineteen who received ten or more treatments showed an average claudication time of more than 4′ 19″, an increase of nearly 300 per cent. The average control claudication time for twenty-four patients tested with normal saline was over 2′ 15″ (these patients had had some previous treatment), and after saline it was more than 2′ 18″. There was, therefore, no significant change.

TABLE I

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 8 PREVIOUSLY UNTREATED PATIENTS WITH UNCOMPLICATED ARTERIOSCLEROTIC VASCULAR DISEASE

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average claudication time
1	1′ 48″	No claud. in 5 min.	2′ 30″	2′ 30″	------
5	44″	1′ 33″	1′ 19″	56″	1′ 39″
6	2′ 37″	1′ 44″	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
24	1′	1′	43″	52″	No claud. in 5 min.
31	1′ 30″	3′ 4″	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
37	1′ 56″	4′ 32″	2′ 15″	51″	------
39	1′ 11″	No claud. in 5 min.	4′ 40″	No claud. in 5 min.	No claud. in 5 min.
43	59″	1′ 36″	------	------	------

*Most of these tests were made after a week or more of treatment.

TABLE II

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 5 PREVIOUSLY UNTREATED PATIENTS WITH ARTERIOSCLEROTIC VASCULAR DISEASE AND OTHER COMPLICATING CONDITIONS

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average claudication time
2	1′ 55″	3′ 14″	1′ 16″	1′ 47″	No claud. in 5 min.
4	1′ 34″	No claud. in 5 min.	1′ 43″	2′ 30″	No claud. in 5 min.
26	1′ 20″	1′ 14″	1′	47″	1′ 37″
34	1′ 23″	3′ 30″	2′ 37″	2′ 37″	4′ 56″
35	2′ 22″	No claud. in 5 min.	------	------	------

*Most of these tests were made after a week or more of treatment.

A record was kept of how far the patients had to walk to produce this syndrome before and during treatment (New York City blocks). The average number of blocks for the entire group before treatment was about two. The average after ten or more treatments was about eight, an increase of 400 per cent (compare with the 300 per cent improvement as measured by the apparatus).

An attempt was made to correlate the claudication time with the oscillometric readings. As one would expect, it was generally true that the lower the oscillometric readings, the shorter the claudication time and the slower the response to therapy.

TABLE III

EFFECT OF 3 C.C. OF DEPROTEINATED PANCREATIC EXTRACT ON THE CLAUDICATION TIME IN 14 PATIENTS WITH ARTERIOSCLEROTIC VASCULAR DISEASE, ALL OF WHOM HAD BEEN TREATED PREVIOUSLY BY OTHER MEANS. SOME OF THE PATIENTS HAD COMPLICATING DISEASES, AND SOME HAD NOT.

IMMEDIATE RESPONSE			SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
Case No.	Average time before DPX	One-half hr. after DPX	Average time before saline	One-half hr. after saline	Average claudication time
3	94″	2′ 11″	1′ 56″	1′ 14″	No claud. in 5 min.
7	35″	1′ 14″	1′ 9″	1′ 46″	1′ 29″
9	1′ 5″	1′ 42″	1′ 10″	2′ 11″	3′ 54″
13	1′ 29″	No claud. in 5 min.	2′ 15″	2′	4′ 47″
14	44″	47″	1′ 2″	1′ 17″	No claud. in 5 min.
18	2′ 5″	1′ 10″	2′ 49″	2′ 39″	3′ 55″
19	2′ 13″	No claud. in 5 min.	2′ 30″	2′ 35″	No claud. in 5 min.
20	1′ 46″	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.	No claud. in 5 min.
22	3′ 6″	No claud. in 5 min.	1′ 12″	1′ 45″	No claud. in 5 min.
25	1′ 29″	2′ 29″	2′ 30″	2′ 40″	No claud. in 5 min.
28	2′ 30″	No claud. in 5 min.	2′ 30″	2′ 30″	------
33	51″	1′ 35″	49″	50″	------
36	59″	2′ 58″	1′ 15″	1′ 8″	------
42	1′ 2″	1′ 33″	------	------	------

*Most of these tests were made after a week or more of treatment.

DISCUSSION

In reviewing Table IV it should be noted that the previously treated group had already been on a control period of routine therapy, including warm baths, abstinence from tobacco, etc., plus a variety of other measures. This group showed, nevertheless, about the same response after treatment with deproteinated pancreatic extract as the previously untreated groups.

TABLE IV

SUMMARY OF THE RESULTS IN 27 PATIENTS OF TREATING INTERMITTENT CLAUDICATION SECONDARY TO ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE WITH DEPROTEINATED PANCREATIC EXTRACT

CLAUDICATION TIME AVERAGES†

TYPE AND NO. OF CASES	IMMEDIATE RESPONSE		SALINE CONTROLS*		AFTER 10 OR MORE TREATMENTS
	BEFORE	ONE-HALF HR. AFTER	BEFORE	ONE-HALF HR. AFTER	
8 Untreated Uncomplicated	1′ 26″	2′ 3″†	3′ 4″†	2′ 52″†	4′ 28″† 5 cases 3 cases had less than 10 treat.
5 Untreated complicated	1′ 43″	3′ 55″†	1′ 39″	1′ 55″	4′ 9″† 4 cases 1 case had less than 10 treat.
14 Previously treated with other therapy Complicated Uncomplicated	1′ 32″	2′ 54″†	2′ †	2′ 6″†	4′ 24″† 10 cases 4 cases had less than 10 treat.
TOTALS (27)	27 1′ 34″	27 3′ 1″†	24 2′ 15″†	24 2′ 18″†	19 4′ 19″† 19 cases 8 cases had less than 10 treat.
Extremes	35″ to 2′ 30″	47″ to 5′ plus (9)	49″ to 5′ plus (3)	47″ to 5′ plus (4)	1′ 29″ to 5′ plus (12)

*Most of these tests were made after a week or more of treatment.

†These averages include cases in which there was no claudication in 5 minutes, and therefore are minimum figures. The true averages would in every case be greater.

Three cubic centimeters of deproteinated pancreatic extract, given intramuscularly on alternate days, appears to be the most satisfactory dose. Larger doses did not, in our experience, seem to produce more beneficial results nor a more prolonged action. Further studies on dosage might be worth while. No untoward reactions have been noted in giving more than 1,000 injections of this substance. It has been

given intravenously to twenty of our patients without severe systemic reactions. We do not advocate its intravenous use at this time, but mention this observation only to emphasize the lack of toxicity. Because of the high protein content of previously used pancreatic extracts, intravenous injections have been definitely associated with risk. The fact that protein is practically absent from this preparation eliminates this danger. Further studies concerning this mode of administration will be reported in the near future.

The mechanism of the action of pancreatic tissue extracts has never been satisfactorily explained, although a hormonal or replacement action similar to that of insulin is the most popular theory today. Assay methods on animals, in which its antagonistic action to adrenalin has been demonstrated, indicate a vasodilatation factor. This effect has not been noted in man. We are at present engaged in studies which may clarify this problem.

The ergometer demonstrated improvement in certain instances in which the patient stated that he had not been benefited. Of 100 patients followed for a period of four to six months while under treatment with deproteinated pancreatic extract, seventy-four reported definite clinical improvement. Many of these were not checked with the ergometer. The other twenty-six failed to show sufficient improvement to warrant continued use of the extract. Spontaneous improvement and regression are common in this condition. It is only by studying a group of patients over a long period of time, and by using a standard method of testing, that conclusions may be drawn as to the value of anything which may be used in the treatment of intermittent claudication due to peripheral arteriosclerosis.

Further refinement and analysis of these extracts may produce fractions that are therapeutically more potent than this one.

SUMMARY

(1) We have described an apparatus to measure claudication time. (2) Following one injection of deproteinated pancreatic extract, twenty-three of a series of twenty-seven patients with arteriosclerosis obliterans showed an improvement (prolongation) of their claudication time. This initial response was in most instances temporary. (3) Following ten or more injections of deproteinated pancreatic extract, nineteen patients showed improvement in their claudication time. (4) After a series of ten or more treatments, the claudication time was, in this series, prolonged to an average of more than three times that of the control tests. (5) Physiologic saline failed to produce an increase in claudication time under identical conditions (6) Further studies will be necessary to determine the extent to which improvement may be advanced, and the duration of the favorable effects after cessation of the treatment.

The authors wish to express their appreciation to Dr. John Miller and Miss Ellen McDevitt for their aid in this study.

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ACTIVITIES ASSOCIATED WITH THE ONSET OF ACUTE CORONARY ARTERY OCCLUSION

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INTRODUCTION

IN SEVERAL previous reports,[1-3] based upon an analysis of 800 attacks of coronary artery occlusion, we presented data in support of the belief that acute coronary artery occlusion is not causally related to physical effort or excitement. These reports also reviewed the literature on this subject. In this paper we offer further evidence, based on study of 1,440 attacks, that coronary artery occlusion occurs irrespective of physical activity.

It is important to distinguish clearly between an attack of angina pectoris and one of coronary artery occlusion. The former is definitely related to exertion, meals, excitement, cold. Although coronary sclerosis is the underlying pathologic condition in both angina pectoris and coronary occlusion, the former is a functional syndrome resulting from transient coronary insufficiency, whereas in coronary occlusion the myocardium is severely injured. In an attack of angina pectoris the patient is usually incapacitated for only a few minutes and is as well after the attack as before. When coronary artery occlusion occurs, however, the patient suffers severe, prolonged pain, may collapse, and develops signs of diminished cardiac output and heart failure. If the attack is survived, physical incapacity persists for weeks or months.

We have also excluded cases of myocardial infarction due to coronary insufficiency. In this condition there is no acute occlusion of a coronary artery, but the coronary circulation is impaired, resulting in necrosis of the heart muscle. It occurs usually with aortic stenosis, surgical operations, tachycardia, acute hemorrhage, pulmonary embolism, and other conditions associated with shock. It is conceivable that, when severe coronary artery disease exists, strenuous effort will produce coronary insufficiency and myocardial infarction without actual coronary occlusion. However, this syndrome differs clinically and electrocardiographically from typical coronary occlusion; the two should not be confused. In coronary insufficiency without occlusion the pain is likely to be less severe and prolonged than in typical coronary occlusion, and in the electrocardiogram there is depression of the R-T segment instead of elevation. Coronary insufficiency is an entity in itself and has been described by many authors.[4, 5]

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MATERIAL

Our data have been derived from a study of 1,440 attacks of coronary artery occlusion observed in 1,077 patients. The latter were almost equally divided between patients seen in the wards of The Mount Sinai Hospital, New York, and those observed in a private consultation practice. We have not included compensation cases because a patient seeking compensation is prone to exaggerate his story and to attribute the attack to some particular event.

Our series includes persons in all walks of life and occupations: factory workers and unskilled and skilled laborers, such as tailors, pressers, peddlers, painters, and printers; store workers; "white-collar" men and office workers; business and professional people, such as merchants, bankers, executives, physicians, teachers, lawyers, and engineers; and housewives (Table I). Of the employed (excluding

TABLE I

OCCUPATIONS IN 1040 CASES OF CORONARY ARTERY OCCLUSION

OCCUPATION	NUMBER	PERCENTAGE
Workers and laborers	377	36.2%
Store workers	55	5.3%
"White-collar" and office workers	90	8.7%
Business men	114	11.0%
Professional men	86	8.3%
Housewives	221	21.2%
None, or retired	96	9.2%

housewives and retired persons) 52 per cent were unskilled and skilled workers, 37 per cent were office workers, store workers, and business men, and the remaining 11 per cent were professional people. This occupational distribution is practically identical with that in the general population of New York City (Table II). Coronary artery occlusion, therefore, is no respecter of poor or rich, laborer or sedentary worker.

TABLE II

COMPARISON OF DISTRIBUTION OF OCCUPATIONS AMONG PATIENTS WITH CORONARY OCCLUSION AND IN GENERAL POPULATION

OCCUPATIONS	CORONARY OCCLUSION	U. S. CENSUS N. Y. C., 1930	JEWISH GAINFUL WORKERS
All occupations	722	3,187,459	799,258
Workers and laborers	377 (52%)	1,766,458 (55%)	410,343 (51%)
Store proprietors (retail), "white-collar" and office workers, business men	266 (37%)	1,169,713 (37%)	300,615 (38%)
Professional workers	79 (11%)	251,178 (8%)	88,300 (11%)

We have been able to record the circumstances at the onset of the symptoms of coronary artery occlusion in 930 cases (Tables III and IV). In addition, in 200 cases detailed histories were obtained concerning the patients' activities the whole day before, and even several

TABLE III

ACTIVITIES AT THE ONSET OF CORONARY ARTERY OCCLUSION

ACTUAL ACTIVITY			ASSOCIATED FACTORS				
ACTIVITY	NO.	INCIDENCE	MEALS	EXCITEMENT	OPERATION	INFECTION	MISCELLANEOUS
Sleep	198	22.3%	15	2	9	1	
Rest	277	31.1%	15	17	46	24	3, diabetic acidosis 2, trauma 1, typhoid injection
Mild activity	180	20.2%	25	15	6	5	2, smoking 2, insulin injection
Moderate activity	76	8.5%	3	6	2	2	
Walking	141	15.8%	10	3	0	0	
Unusual exertion	18	2.0%	0	0	0	1	
Undetermined	40		24	9	0	7	0
Unknown	510						
Total	1440		92 (9.9%)	52 (5.6%)	63 (6.6%)	40 (4.3%)	10 (1.1%)

weeks before, their attacks. In these a special questionnaire was used (Table V). Incidentally, the frequency and character of premonitory symptoms were thus determined, and these will be subsequently reported.

Table III shows that the attack occurred during sleep in approximately one-fourth of the cases, and during rest in almost one-third. Thus, 53.4 per cent of all the attacks occurred under conditions of rest and sleep, a percentage that corresponds to the fraction of the day spent in rest and sleep. Twenty per cent of the patients were engaged in mild activity at the time of the attack; that is, they were dressing, standing, talking, sitting in the office, etc. Eight and one-half per cent were doing moderately heavy work, such as painting, baking, driving a car, and 2 per cent were engaged in some unusually severe effort, i.e., swimming, skating, playing football, running, carrying a heavy load. We have grouped the patients who were walking, separately; walking preceded approximately 16 per cent of attacks. Thus, 44.5 per cent of attacks were associated with some mild or moderate activity, or with walking, and only 2 per cent with severe exertion.

In addition to the foregoing activities or inactivity, in 257 attacks an associated factor, such as eating, excitement, a surgical operation, infection, or one of several miscellaneous circumstances, was present. In 92 patients (9.9 per cent) the attack of coronary occlusion was associated with eating, i.e., the closure occurred while the patient was eating, or within one or two hours thereafter. In 37 cases the attack followed a heavy meal, and, in the remainder, a light one. Included in this group are 15 patients who suffered the attack in sleep after a heavy meal, and ten who were stricken while walking directly after a meal. A large number of attacks, although related to a meal, occurred during rest or ordinary mild activity.

TABLE IV

TYPES OF ACTIVITY AT ONSET OF CORONARY ARTERY OCCLUSION (930 ATTACKS)

TYPES OF ACTIVITY	NUMBER	PERCENTAGE
A. Primary Activities (890 attacks):		
1. Sleep	198	22.3%
2. Rest—lying down or sitting up	277	31.1%
3. Ordinary mild activity	180	20.2%
62, in home (dressing, standing, walking about, playing with children, talking, retiring, etc.); 35, in store or office; 14, sitting in car or train; 9, in doctor's office or clinic; 8, doing light housework; 6, getting out of bed; 5, taking showers or bath; 5, getting out of bus or car; 5, playing cards; 4, attending a meeting; 4, sitting in a movie; 2, in restaurant; 21, miscellaneous.		
4. Moderate activity (except walking)	76	8.5%
35, working as laborers (painter, engineer, carpenter, baker, tailor, presser, etc.); 16, driving car; 8, during bowel movement or straining at stool; 6, shopping; 2, coughing; 2, running upstairs; 2, during coitus.		
5. Walking	141	15.8%
107, in street; 11, upstairs; 6, after meals; 5, against cold wind; 4, uphill; 4, downstairs; 2, in snowstorm; 2, carrying ten pounds.		
6. Unusual or severe exertion	18	2.0%
9, during or immediately after sport or games (football, swimming, dancing, skating); 5, lifting or moving a heavy load; 3, running for train; 1, after long automobile ride.		
B. Associated Factors (930 attacks):		
1. Meals	92	9.9%
37, heavy meal; 33, ordinary meal; 22, light meal; 15, in sleep; 10, while walking.		
2. Excitement	52	5.6%
13, gambling or playing cards; 8, during argument; 4, at movies; 3, news of deaths of relatives; 3, fright; 3, at wedding or banquet; 2, making speech; 2, during coitus; 1, at funeral; 13, miscellaneous (emotional upset).		
3. Surgical procedures	63	6.6%
26, laparotomy; 20, genitourinary operation; 7, eye, ear, nose or throat operation; 3, leg operation; 2, thyroidectomy; 1, thoracotomy; 1, tooth extraction; 1, incision of furuncle; 1, paravertebral block; 1, bronchoscopy.		
4. Infection	40	4.3%
14, upper respiratory infections; 6, grippe; 4, cholecystitis; 2, peritonitis; 3, pyelonephritis; 4, pneumonia; 2, appendicitis; 2, sepsis; 3, abdominal suppuration.		
5. Miscellaneous	10	1.1%
3, diabetic acidosis; 2, insulin injections; 2, trauma (1 fall on chest and 1 injury to eye); 2, smoking; 1, typhoid injection.		

TABLE V

ONSET OF CORONARY ARTERY OCCLUSION—QUESTIONNAIRE

Name	Adm. No.	Age and Sex	Occ.
Date of onset		Hour of onset	
Description of work:		Type, hours, rest, etc.	

History of angina pectoris, dyspnea, etc., with precipitating factors:
Activities 4 weeks preceding onset:
Premonitory symptoms and activities preceding and attending them (dates):
Onset of symptoms of attack and activities preceding and attending them (dates):
Summary activity during onset, preceding 24 hours, week, 4 weeks:
Tobacco Liquor
Remarks:

Fifty-two attacks (5.6 per cent) set in during excitement; that is, while gambling, or during or directly after an argument, or during or after fright, etc. The great majority of these patients were at rest or engaged in ordinary mild activity at the time of the emotional upset.

Sixty-three attacks (6.6 per cent) occurred within three weeks following a surgical operation, and infections of various types preceded the attack in forty cases (4.3 per cent). These included upper respiratory infection, cholecystitis, peritonitis, and pneumonia. Approximately half of these cases are also included in the postoperative group.

A small miscellaneous group comprises three attacks during diabetic coma, two after insulin injections, two while smoking, and one soon after a typhoid vaccine injection. Two attacks were associated with trauma—in one case a fall, and in the other a blow on the eye. In twelve cases the onset of the occlusion was manifested by repeated attacks of angina pectoris of increasing severity, thus making it difficult to determine just when the occlusion occurred. In eight cases the occlusion was silent; there was no history of pain, pressure, or other symptoms.

There was no preponderance of attacks in any particular period of the day (Table VI). Of the 722 attacks in which the time of onset

TABLE VI

TIME OF ONSET OF CORONARY ARTERY OCCLUSION IN 722 ATTACKS

PERIOD OF THE DAY	ATTACKS	INCIDENCE
Morning (7 A.M.-1 P.M.)	209	28.9%
Afternoon (1 P.M.-7 P.M.)	167	23.1%
Total (7 A.M.-7 P.M.)	376	52.0%
Evening 7 P.M.-1 A.M.)	162	22.5%
Night (1 A.M.-7 A.M.)	184	25.5%
Total (7 P.M.-7 A.M.)	346	48.0%

was known, 23.1 per cent occurred in the afternoon (1 P.M. to 7 P.M.), 22.5 per cent in the evening (7 P.M. to 1 A.M.), and 25.5 per cent in the night (1 A.M. to 7 A.M.). A slightly greater number occurred during the morning hours (7 A.M. to 1 P.M., 28.9 per cent). Fifty-two per cent of the attacks began during the daytime, and 48 per cent during the night. The exact hour of day when the attack occurred was ascertained in 471 cases (Table VII). Although the incidence of coronary occlusion was greatest at 2 A.M. and 10 P.M., it seems that no one hour was especially important.

TABLE VII

TIME OF ONSET OF CORONARY ARTERY OCCLUSION IN 471 ATTACKS

HOUR	NO.	HOUR.	NO.
1 A.M.	21	1 P.M.	23
2	37	2	19
3	19	3	17
4	11	4	14
5	15	5	15
6	19	6	20
	122 (25.9%)		108 (22.9%)
7 A.M.	23	7 P.M.	16
8	18	8	15
9	20	9	16
10	19	10	30
11	23	11	25
12	18	12	18
	121 (25.7%)		120 (25.5%)

DISCUSSION

In reviewing the data on the activities at the onset of the occlusion it will be seen that 53.4 per cent of the attacks occurred during rest and sleep. This association is fortuitous, since one spends about half the day in these states. The same conclusion holds true for physical activity, including mild and moderate exertion and walking, which attended 44.5 per cent of the attacks, since at least two-fifths of the day is spent in such pursuits. Hence the onset of the attack did not depend on the state of physical activity or inactivity of the body. The findings were similar in the 200 cases in which a detailed history was obtained of the patients' activities for days, and even weeks, prior to their attacks.

The factor of unusual or severe exertion must be discussed in some detail. Twenty-five compensation cases which came under the observation of the senior author in private practice were omitted from our series because in such cases the patient's story is likely to be colored and exaggerated. These patients usually attribute their attacks to lifting or moving a heavy load. With the omission of this group, barely 2 per cent of all of the attacks were associated with some unusual effort, such as lifting a heavy load, playing football, swimming,

dancing, running for a train, etc. It may be argued that, although 2 per cent is a small number, the severe effort was a factor in precipitating the coronary occlusion in this small group. However, even the most sedentary person frequently performs some unusual effort during the day; nearly everyone has occasion to run, climb stairs, rush for a bus or train, tug at a drawer, lift a stuck window, park a car, remove a tire from a car, carry a heavy bag or weight, move a piece of heavy furniture, dance, or play golf. Were effort a factor, every day thousands of men and women over the age of 45 or 50 years with coronary artery disease would sustain attacks associated with severe exertion, and the percentage in our series would be much greater than 2 per cent.

It is important to point out that in 60 cases the attack occurred when the patient had been in bed for weeks or months with a chronic illness or a previous coronary occlusion. In these cases there can be no question of effort at any time preceding the attack.

Premonitory complaints, such as pain or pressure in the chest, shortness of breath, and weakness, were noted in 80 of 170 cases in which the history was adequate. These premonitory symptoms appeared several hours or days before the actual attack, during rest or some ordinary activity. As far as we could ascertain, they were not related causally to severe exertion.

Two other groups of data make the conclusion inescapable that activity is of no importance in the precipitation of coronary occlusion. Thus, the period of day and the actual hour when the occlusion occurred played no role, since the number of attacks in the working or play hours did not exceed those in the evening or night hours. In fact, 10 P.M. and 2 A.M. were the peak hours, and certainly the majority of people are resting or sleeping at these times.

The occupational distribution in our cases was practically the same as that in the general population of New York City. Although in one authoritative report[6] the author maintained that there is a higher incidence of coronary occlusion in the upper strata of society, most figures, including ours, demonstrate that coronary arteriosclerosis affects all classes equally.

It is obvious that when acute myocardial infarction has already occurred, effort may produce pain. It is even possible that strenuous effort may induce pain during the formation of the occluding thrombus, a process which occurs over an interval, and thus make the patient aware of the condition. However, the effort does not play a role in the actual pathogenesis of the occlusion. Trauma, too, may seriously damage the heart and aorta, but it may be repeated that in this paper we are concerned only with the cause of classical coronary artery occlusion.

In recent years, pathologists[7-10] have emphasized the fact that the thrombus in a coronary artery often results from an intimal hemorrhage into an atherosclerotic plaque. This has been used as corroborative evidence by those (e.g., Paterson[11]) who maintain that effort and excitement may lead to coronary artery occlusion; they assume that the transitory rise of blood pressure which accompanies the exertion or excitement may cause intimal hemorrhage. Such an assumption is refuted by several observations. Capillary, and even intimal, hemorrhages occur in shock, in which the blood pressure drops to very low levels. Furthermore, Winternitz, et al.,[9] injected dye into sclerotic coronary arteries at pressures varying from 500 to 1000 mm. Hg without producing rupture of the intimal capillaries. Surely the pressure in the coronary arteries and capillaries during life is very much lower than this, so that hypertension cannot be a factor in intimal hemorrhage.

Whatever the actual pathogenesis of coronary artery occlusion may be, our clinical data appear to us to exclude exertion as a factor. Furthermore, there is no evidence that intimal hemorrhage into a plaque is precipitated by effort; it is part of a degenerative process resulting from pre-existent and progressive atherosclerosis.[12] It appears at the site of the most advanced arteriosclerosis and is probably unrelated to external influences. In fact, intimal hemorrhage was just as frequent a post-mortem finding in our patients who had been confined to bed for weeks as in those who were active before the coronary occlusion.

It is important to consider the relationship of coronary occlusion to meals, which have been assumed to be a precipitating factor. About 10 per cent of the attacks in our series set in during or after a meal; this includes attacks which occurred as long as two hours after a meal, providing it was a heavy one. Considered in this way, the period of day in relation to the three meals is much more than 10 per cent; hence, one must conclude that in our series the relationship of attacks to meals was fortuitous.

Only 5.6 per cent of the attacks of coronary occlusion in our series showed some association with emotion, in spite of the fact that all of us repeatedly experience some degree of excitement, whether it is a fright, an argument, or a death in the family. Were emotion and excitement factors, one should find them very commonly associated with attacks of coronary occlusion; indeed, it might be dangerous for people over fifty to read a newspaper or listen to the radio.

One cannot rule out infection as a factor in our cases of coronary artery occlusion. It was a frequent complication, particularly in the postoperative cases. Among the patients who had not been operated on, there were 23 instances in which an upper respiratory infection,

grippe, or other acute disease, was present for several days preceding the attack. It will be necessary to gather data from a larger series of cases before a definite conclusion on this point can be reached. The relation of surgery to coronary artery occlusion has been discussed in a previous publication.[13]

SUMMARY

1. One thousand four hundred and forty attacks of coronary artery occlusion were analyzed from the standpoint of the patients' activities preceding the attacks, the time of day when the attacks occurred, the patients' occupations, and other associated factors.

2. The distribution of occupations in this series of cases was approximately the same as that in the general population; therefore, occupation and social status did not predispose to coronary occlusion.

3. The circumstances preceding the onset of symptoms in 890 cases were: sleep, 22.3 per cent, rest, 31.1 per cent, mild activity, 20.2 per cent, moderate activity, 8.5 per cent, walking, 15.8 per cent, and unusual exertion, 2.0 per cent.

4. Correlation of these percentages with the number of hours spent daily by the ordinary person in the same occupations indicated that the circumstances were coincidental and that none of them was causally related to the coronary occlusion. Coronary occlusion occurs irrespective of the state of physical activity of the body.

5. Associated factors in 930 cases were: meals, 9.9 per cent, emotional excitement, 5.6 per cent, surgical operation, 6.6 per cent, infection, 4.3 per cent, and miscellaneous factors, 1 per cent. It was concluded that, with the possible exception of surgical procedures, these factors did not play a role in the pathogenesis of coronary occlusion. Only two attacks of coronary occlusion were associated with trauma.

6. Detailed histories of the activities and emotional state of patients for hours, days, and weeks preceding attacks confirm the belief that physical activity and excitement are not factors in the onset of coronary occlusion.

7. Sixty patients sustained an attack of coronary occlusion after having been bedridden for weeks or months because of some chronic illness.

8. The time of onset of the attack was ascertained in 722 cases. Equal numbers occurred during the afternoon, evening, and night, and a slightly greater number during the morning. The attacks were well distributed throughout all the hours of the day, with peaks at 2 A.M. and 10 P.M. This also indicates that activity is not a factor in the precipitation of coronary occlusion.

9. Premonitory symptoms of the attack, such as chest pain, dyspnea, or weakness, were present in 80 of 170 cases in which these symptoms were investigated.

10. There is no evidence that physical effort or excitement produces intimal hemorrhage in the coronary arteries, which is the usual forerunner of thrombosis and occlusion. Intimal hemorrhage is the end result of the progressive, degenerative arteriosclerotic process and is probably a fortuitous event. It was found at necropsy as frequently in patients who had been bedridden prior to the occlusion as in those who were physically active.

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CONVALLAN IN CARDIAC THERAPY

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CONVALLARIA MAJALIS, or lily-of-the-valley, has been known for many years as a cardiac tonic and diuretic. However, convallaria has played a very small role in the therapy of cardiac disease because the preparations available have not been standardized and are often inert.

Until recently the preparations used were mainly infusions and fluid-extracts of leaves, roots, or of the whole plant. Marvin and White,[1] in 1921, showed that the activity of convallaria is due to certain glucosides which resemble digitalis. W. Karrer,[2] in 1929, isolated a crystalline glucoside of convallaria by extraction with chloroform and named it convallatoxin. An assay of this substance showed that it contained three million frog doses* per gram. Straub,[3] in 1937, described an extract prepared by treating an aqueous solution of convallaria with colloidal iron hydroxide and concentrating the filtrate to a powder. This extract he named "convallan." Straub's convallan was found to consist of 20 per cent convallatoxin and 80 per cent "convallamarin complex." Physiologic assays showed that convallan contained 4000 to 8000 frog doses per gram.

Von Bergmann[4] studied the pharmacologic properties of convallan and found that its activity, as measured in frog doses, showed that it stood between digitalin and strophanthin in therapeutic effect, but was much less toxic than either.

The findings of Von Bergmann were confirmed by Büttner,[5] who found from his clinical studies that the minimum effective dose was 3000 frog units, that the maximum dose which could be employed was 20,000 units, and that doses of 12,000 frog units may be administered daily with safety. Büttner also found that convallan had little, if any, cumulative action, and that it may be given before or after digitalization with complete safety. Büttner also noted that the pharmacologic action of convallan in large doses was essentially the same as that of digitalis and strophanthin. However, small doses produced a remarkable diuretic effect without causing heart block or increasing the degree of an already existing block.

This interesting observation suggested its use in patients suffering from cardiac failure associated with varying degrees of heart block.

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*One frog dose is the smallest amount of a drug, per gram of animal, which will kill a frog when injected into the ventral lymph sac.

The dosage employed in this group of cases was largely empirical and was determined by the pharmacologic effect obtained in the individual patients.

REPORT OF CASES

CASE 1.—B. W., a colored man, aged 82 years, was admitted to the hospital July 13, 1938. The patient, on admission, had evidence of arteriosclerotic heart disease, with severe dyspnea, orthopnea, ascites, bilateral hydrothorax, and marked edema of the ankles and feet. On admission, the electrocardiogram (Fig. 1) showed left bundle branch block. The patient received 2000 F. D.* of convallan daily for four

Fig. 1.

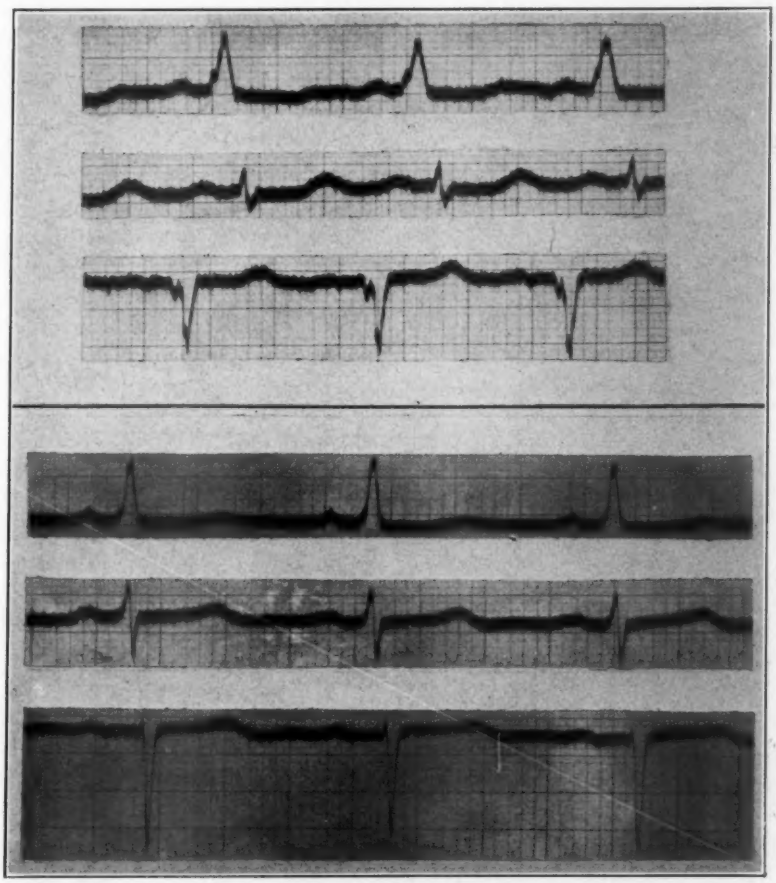

Fig. 2.

Fig. 1.—Case 1, taken on admission into the hospital, showing intraventricular conduction impairment.

Fig. 2.—Case 1, taken nineteen days after the admission electrocardiogram (Fig. 1). Note improvement in intraventricular conduction, slower rate, and repolarization.

days. The dose was then increased to 3000 F. D. for three days, after which he was placed on a maintenance dose of 2000 F. D. daily. There were a rapid loss of anasarca, disappearance of dyspnea, and slowing of the pulse rate. The patient was

*F.D., frog dose.

Fig. 3.

Fig. 4.

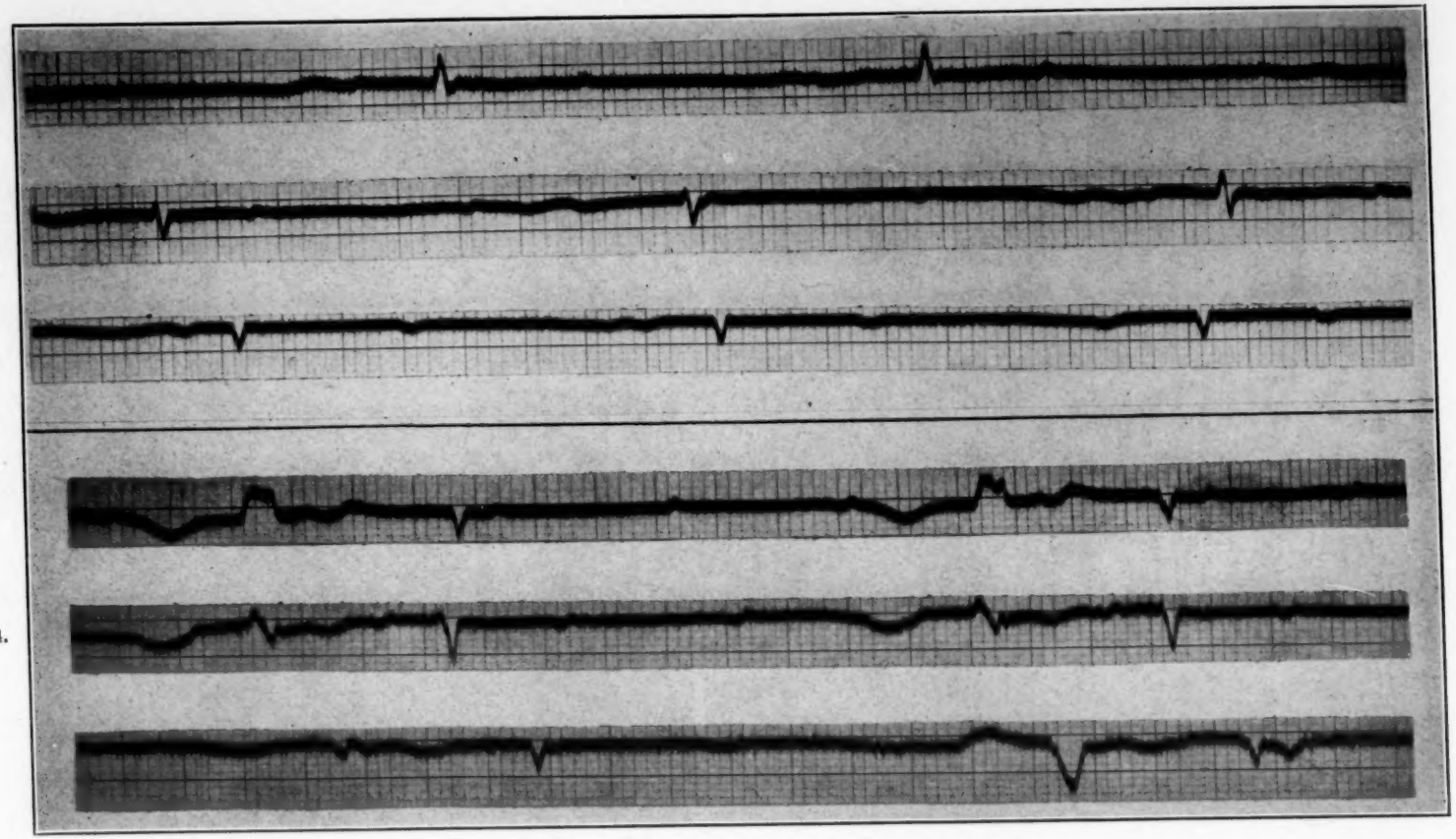

Fig. 3.—Case 2, taken on admission into the hospital, showing complete heart block and bigeminy.
Fig. 4.—Case 2, taken six days after electrocardiogram in Fig. 3. Note absence of bigeminy and more rapid ventricular rate.

dismissed nineteen days after admission entirely free from edema. An electrocardiogram (Fig. 2) taken Aug. 1, 1938, showed improvement in the auriculoventricular conduction. Ten months after dismissal from the hospital the patient continues in fair condition, having slight edema only occasionally.

CASE 2.—J. R., a white man, aged 79 years, with arteriosclerotic heart disease, was admitted to the hospital Dec. 8, 1938, showing ascites, bilateral hydrothorax, and edema of the legs. On admission, the electrocardiogram (Fig. 3) showed complete A-V dissociation with bigeminy. The patient received 3000 F. D. of convallan daily, and the edema and dyspnea disappeared rapidly. The electrocardiogram (Fig. 4) which was taken Dec. 14, 1938, showed complete A-V dissociation with an auricular-ventricular rate ratio of 2:1, and there was none of the previous bigeminy. The patient was dismissed from the hospital on a maintenance dose of 3000 F. D. daily, and four months later he was still free of edema.

Fig. 5.

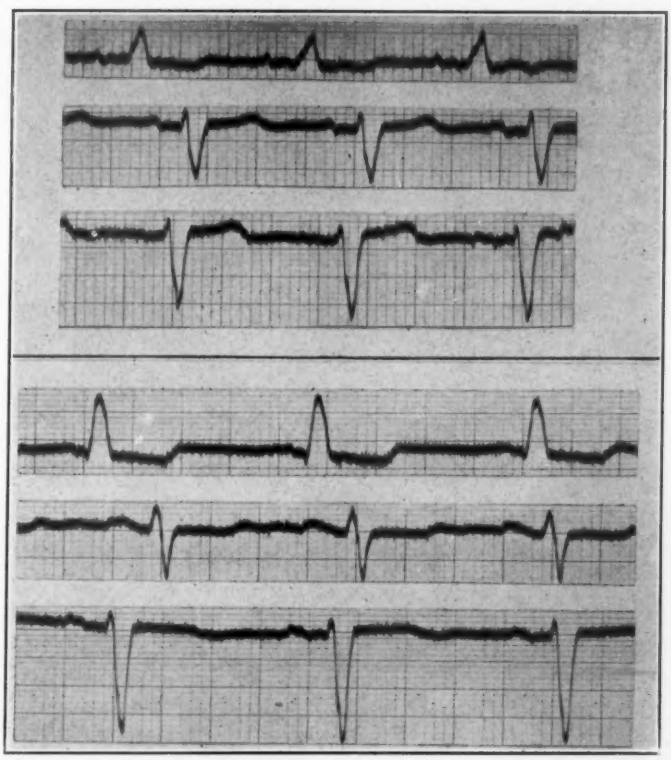

Fig. 6.

Fig. 5.—Case 3, taken before convallan therapy.
Fig. 6.—Case 3, taken after three months of 3,000 F.D. of convallan daily.

CASE 3.—P. I., a white woman, aged 60 years, suffering from arteriosclerotic heart disease, was admitted to the hospital May 31, 1938. At the time of admission she showed marked dyspnea, anasarca, and edema of the extremities. The patient received digitalis from June 2, 1938, to Jan. 6, 1939, with no noticeable improvement. She then received convallan in doses of 2000 F. D. daily, and in eighteen days she lost 23½ pounds and showed remarkable improvement. The electrocardiogram

(Fig. 5), taken seven days after admission to the hospital, after she had received digitalis, showed no change from previous electrocardiograms; bundle branch block was present. An electrocardiogram taken after three months of convallan therapy (Fig. 6) showed no increase in the degree of heart block, and the patient's condition was much improved.

CASE 4.—P. H., a white man, aged 74 years, was admitted to the hospital Dec. 28, 1938, showing marked dyspnea, gallop rhythm, and edema of the ankles. The patient was found to be suffering from hypertensive cardiovascular disease with cardiac failure. The electrocardiogram (Fig. 7), taken Dec. 29, 1938, showed prolongation

Fig. 7.

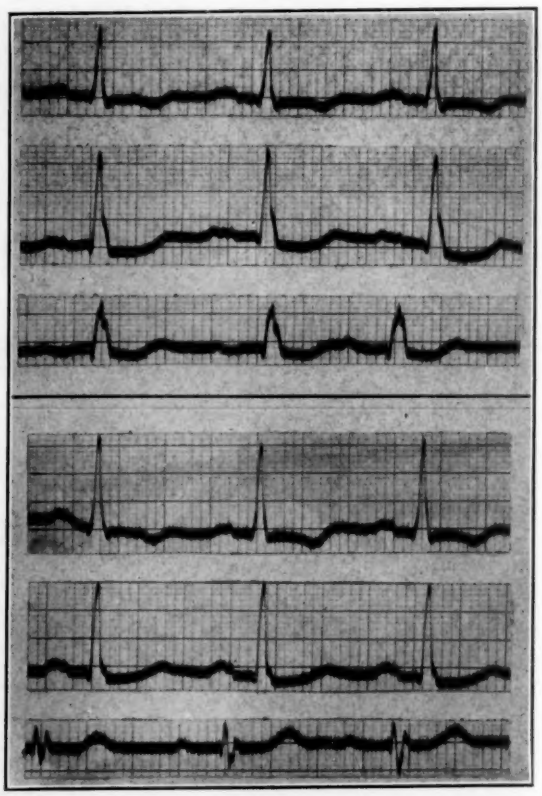

Fig. 8.

Fig. 7.—Case 4, taken on admission to hospital. No axis deviation.

Fig. 8.—Case 4, taken thirty days after admission. Left axis deviation; change in T_1, T_2, and T_3.

of conduction time and some depression of the S-T segments in Leads II and III. He received 3000 F. D. of convallan daily, was promptly relieved of edema and dyspnea, and the gallop rhythm disappeared. The blood pressure, however, remained unchanged. An electrocardiogram (Fig. 8) taken Jan. 30, 1939, showed little change in the heart rate but distinct improvement in auriculoventricular conduction and beginning left axis deviation. This patient was placed on a maintenance dose of 3000 F. D. daily, and four months later he showed continued improvement.

CASE 5.—G. F., a white woman, aged 47 years, a sufferer from hypertensive cardiovascular disease for several years, was admitted to the hospital Jan. 14, 1938, complaining of nausea and vomiting. She showed marked orthopnea and dyspnea. The electrocardiogram (Fig. 9), made Jan. 15, 1939, showed left bundle branch block. The patient was digitalized, but her condition did not improve; after bed rest for nine weeks, the pulse rate remained between 110 and 130, and marked dyspnea was still present. She was then given 3000 F.D. of convallan daily for four days and showed very marked symptomatic improvement. She was dismissed on a maintenance dose of 2000 F. D. daily. The electrocardiogram (Fig. 10) taken April 7, 1938, showed left axis deviation, which was not present in the first electrocardiogram.

Fig. 9.

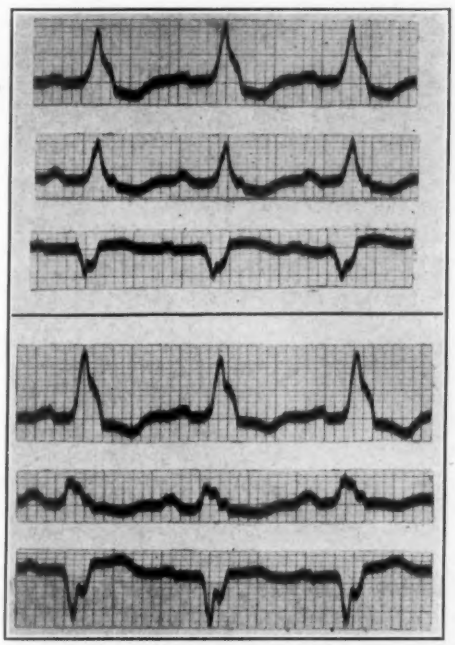

Fig. 10.

Fig. 9.—Case 5, on admission to the hospital. Left bundle branch block. No axis deviation.

Fig. 10.—Case 5, three and one-half months later. Left axis deviation.

This group of cases is a selection from a much larger number in which convallan was used in treatment. In a number of cases of valvular heart disease with marked decompensation, favorable clinical results were obtained, but results no better, and often not as good as those gained by using digitalis. Two patients with lipoid nephrosis were treated with convallan; one responded with complete disappearance of the edema, while the other was unaffected by the drug.

Our impression, after a two-year experience with convallan, is that it can be employed, often with much benefit, in cases of heart block or bundle branch block with cardiac failure in which the administra-

tion of digitalis is not advisable. We have been very much impressed by the marked diuretic effect which convallan produces in certain patients.

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CAPILLARY RUPTURE WITH INTIMAL HEMORRHAGE AS A CAUSE OF PULMONARY THROMBOSIS

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THE differentiation between primary thrombosis of the pulmonary artery and embolism due to the transport of thrombus material from a distant site is difficult. When the occluding masses occupy the entire arterial lumen, as they usually do, one is forced to consider them as emboli, even when the site of primary thrombosis cannot be found. However, small mural thrombi which occupy only a part of the lumen and are firmly attached to the arterial wall can be regarded as primary depositions. Two such cases of thrombosis, in situ, of the pulmonary artery and its branches are reported here. It was interesting to note that the mechanism of thrombus deposition in each case appeared identical with that which I have described in sclerotic coronary arteries,[1] namely, capillary rupture with intimal hemorrhage into an atherosclerotic plaque.

CASE REPORTS

Case 1.—A 64-year-old woman was admitted to hospital four months before death, complaining of weakness in both legs, pain in the back, and debility. Examination revealed a severe hypochromic anemia, marked kyphosis of the lower dorsal vertebrae, and paraplegia. She grew worse steadily, and developed signs of bronchopneumonia as a terminal feature. Decubitus ulcers were present.

Autopsy revealed almost complete destruction of the tenth, eleventh, and twelfth thoracic vertebrae by a tuberculous process, with secondary infection by Gram-negative bacilli. The spinal cord at the level of the eleventh thoracic vertebra was compressed and thinned out to approximately one-third its normal width. Acute, bilateral bronchopneumonia was the immediate cause of death. Additional autopsy findings were leiomyoma of the uterus, bilateral cortical adenomata of the adrenal glands, old pleural adhesions, and severe hypochromic anemia.

The apex of the left ventricle contained a firmly adherent mural thrombus, the center of which was liquefied and showed Gram-negative bacilli on direct smear. No infarction, old or recent, was noted in the adjacent myocardium. The aorta, coronary arteries, and the pulmonary artery and its main branches showed a moderate grade of atherosclerosis. In the pulmonary artery there were numbers of small, slightly raised, yellowish flecks, the process extending down as far as the tertiary branches. In one of the latter, on the right side, a pedunculated mass of thrombus was attached firmly to the apex of an elevated plaque. This thrombus measured approximately 6 by 2 by 2 cm.; it was pear-shaped, and its pedicle was quite narrow. The thrombus occupied about one-fourth of the lumen of the artery. The entire thrombus and the adjacent part of the arterial wall were embedded in paraffin in one block, and sectioned serially at intervals of 100 μ, the sections being cut longitudinally. The sections were stained with hematoxylin and eosin and with Perle's stain for iron pigment.

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Microscopically, the intima of the artery showed a diffuse thickening of the fibrous "endarteritic" variety, but at the point of thrombus attachment there was an atheromatous plaque into which hemorrhage had occurred. The hemorrhage appeared to vary in age in different parts of the atheromatous plaque; the central portion showed intact red cells, while at the periphery hemosiderin could be demonstrated with Perle's stain. The intervening space was occupied

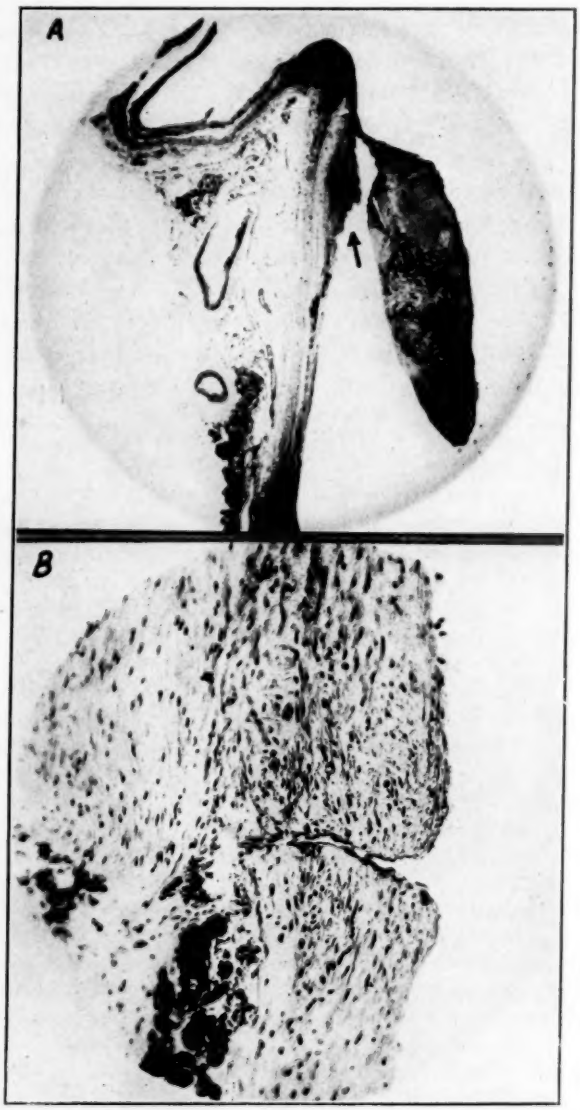

Fig. 1.—*A*, a longitudinal section through a branch of the pulmonary artery in Case 1. A pedunculated thrombus projects into the lumen and is attached to the arterial wall at a point (shown by the arrow) where hemorrhage had occurred into an atherosclerotic plaque. The thrombus was partially separated at this point during the process of sectioning. Hematoxylin and eosin stain was used. ×18.
B, a section through the same branch artery, showing a small capillary arising from the lumen and penetrating the intima. Hematoxylin and eosin stain was used. ×130.

by homogeneous material which stained pink with eosin and resembled "fibrinoid" material. The pedicle of the thrombus was attached to the apex of the hemorrhagic focus, and here it showed advanced organization and hemosiderin production (Fig. 1*A*). The body and tip of the thrombus were of more recent origin, consisting of skeins of fibrin and platelets with enmeshed red cells and leucocytes. No intimal capillaries could be made out in the area of intimal hemorrhage, but farther down in the artery a small capillary was noted, arising from the lumen and penetrating the thickened intima (Fig. 1*B*).

CASE 2.—An 81-year-old man was admitted to hospital five weeks before death, complaining of frequency of micturition of six years' duration, and of a painful swelling in the perineum for one month. On examination, the prostate gland was found to be symmetrically enlarged, firm, and smooth. There was a painful, indurated swelling in the perineum which displaced the scrotum forward, and extended from the left inguinal region to within half an inch of the anus. Two days after admission this swelling was incised, and a large amount of purulent material evacuated. Cultures of this material grew a nonhemolytic streptococcus, *Staphylococcus aureus*, and *B. coli*. Two weeks later cystostomy was performed. Subsequently he grew worse. A spreading ulcer developed at the point where the perineal abscess had been drained. At no time in the postoperative period were there any signs or symptoms referable to the lungs.

Fig. 2.—A slightly enlarged photograph of a tertiary branch of the pulmonary artery in Case 2. Most of the intimal hemorrhages are situated about the orifices of branch arteries. The endothelium over some of the hemorrhages is intact, while over others it is ulcerated and replaced by mural thrombus.

Autopsy revealed an adenomyoma of the prostate gland, acute necrotic cystitis, acute and chronic osteomyelitis of the pubic bone, brown atrophy of the heart, and a moderate grade of cerebral edema.

The right common iliac vein and the right external iliac vein were completely occluded by an adherent mass of thrombus. The pulmonary artery and its main branches showed numerous, slightly raised, yellowish, atherosclerotic plaques. In addition, the intimal surface of many of the secondary, tertiary, and smaller branches of the pulmonary artery showed numbers of greyish-brown, irregularly

rounded swellings, most of which were situated close to the orifices of branch arteries (Fig. 2). They varied between 1 mm. and 1 cm. in diameter. The endothelial surface over some of the swellings was intact; over others it was ragged and apparently ulcerated, while over a few thrombus was attached to it. One branch artery was almost completely occluded by thrombus. Six of these lesions

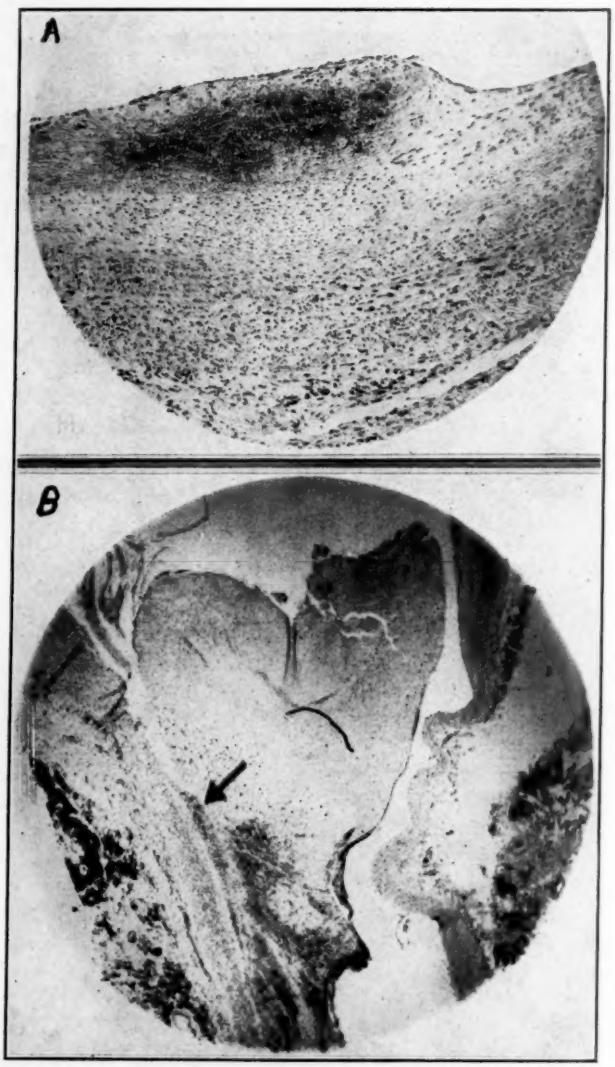

Fig. 3.—*A*, a section of one of the intimal hemorrhages in Case 2. The endothelium and the superficial intimal layers are intact and are elevated by the hemorrhage. Hematoxylin and eosin stain was used. ×55.
B, a longitudinal section through a small branch artery in Case 2. The lumen is almost occluded by a thrombus which is attached at a point (marked by the arrow) where hemorrhage had occurred into an atherosclerotic plaque. Hematoxylin and eosin stain was used. ×20.

were embedded in paraffin and sectioned serially at intervals of 100 μ. The sections were stained with hematoxylin and eosin. Three others were sectioned by freezing, and the sections were stained with Sudan III and hematoxylin.

Microscopically, each of the areas of intimal discoloration was found to represent a hemorrhage into the subendothelial tissues. Intact red cells could be seen in most of the hemorrhages; organizing blood clot was present in some; and occasionally hemosiderin could be demonstrated, particularly at the outer edge of the hematoma. Small capillaries lying in proximity to the extravasated blood and to the lumen of the artery were seen in several of the sections. The endothelium and the subendothelial tissues overlying the hemorrhages were intact in a few instances (Fig. 3*A*), and in these there was no evidence of thrombosis. However, in the majority the superficial layers could not be made out, the area of hemorrhage gradually merging into a ragged mass of thrombus which projected slightly into the lumen of the artery. In one instance the lumen of a branch artery was almost completely occluded by a large thrombus which was attached to the apex of a small atherosclerotic plaque into which hemorrhage had occurred (Fig. 3*B*). The frozen sections which were stained with Sudan III and hematoxylin showed stainable fat intermingled with blood in most of the intimal hemorrhages.

COMMENT

Because most of the pulmonary thrombi in these two cases occupied only a small part of the arterial lumen, and because they were firmly attached to the intima by organizing tissue, one can safely assume that they were formed in situ. The principal causes of pulmonary thrombosis, as given in the literature, are stasis of blood in aneurysmal sacs, inflammatory lesions of the arterial wall (either primary arteritis or secondary arteritis due to the spread of inflammation from the adjacent lung tissue), and atherosclerosis with the formation of atheromatous "ulcers." Less commonly, other conditions may act as contributary causes—increase in the blood calcium, polycythemia, dehydration and anoxemia, and myocardial insufficiency with consequent slowing of the pulmonary circulation. From the findings in the two cases reported here, it would appear that capillary rupture with hemorrhage into atherosclerotic plaques should be included in the list of principal causes.

The intimal hemorrhages in these two cases were similar in structure to those previously described in sclerotic coronary arteries and in association with coronary thrombi.[1] They had occurred into atheromatous foci, and in several instances small capillaries which arose from the arterial lumen lay in proximity to the extravasated blood. It is admitted that intimal hemorrhages of the coronary arteries result from the rupture of intimal capillaries.[1, 2, 3] Intimal hemorrhages in the pulmonary artery and its branches can be considered to be of similar origin. Furthermore, because the intimal hemorrhages were found at the point of attachment of all the pulmonary thrombi in the two cases, it would appear that the liberation of thromboplastic substances, either from the hemorrhages proper, or from other lesions which are secondary to capillary rupture, was responsible for thrombosis.

I have already suggested that the main causes of capillary dilatation and rupture in sclerotic coronary arteries, in the order of their importance, are (1) high intracapillary blood pressure due to persistent or

transient hypertension, (2) softening by atheroma of the stroma supporting the capillary wall, and (3) increased capillary fragility. There is reason to believe that this order of causative factors should be reversed in cases of pulmonary thrombosis.

The normal systolic blood pressure in the pulmonary artery is said to be 30 to 40 mm. Hg, a pressure which is low compared to that in the aorta and its main branches; and there were no findings in the two cases reported here to suggest that the intrapulmonary pressure had been abnormally raised for any length of time. That is to say, there were in neither case any pathologic lesions such as mitral stenosis, brown induration of the lungs, hypertrophy of the right ventricle, or chronic passive congestion of the liver and spleen, all or some of which are usually associated with long-standing high pressure in the lesser circulation. Except for the possibility of a sudden and transient increase in the intrapulmonary pressure in these two cases, a highly improbable condition, the factor of increased intracapillary pressure in the production of dilatation and rupture of intimal capillaries in the pulmonary artery appears to be of little importance.

The influence of atheromatous degeneration in the production of intimal hemorrhages in the pulmonary circulation is difficult to estimate. Softening is a physical character of atheroma, and it is assumed that the softening process allows the wall of a capillary to dilate and rupture as the result of the pressure within its lumen. While both gross and microscopic evidence of atherosclerosis was present in the pulmonary artery in each of the cases reported here, the lipoid deposits were not nearly so massive as those affected by intimal hemorrhage in the coronary arteries. Indeed, most of the hemorrhages in Case 2 had occurred into the more superficial subendothelial tissues. It would appear, therefore, that the rupture of the intimal capillaries in these two cases cannot be laid to overdilatation from increased intracapillary pressure or from excessive atheromatous degeneration. Inasmuch as other information was lacking, it was probably due to increased capillary fragility. It is known that the walls of capillaries become more fragile with advancing age;[4] one of the patients was 81 years old, and the other, while only 64, appeared prematurely aged, presumably as the result of a long-standing tuberculous infection. Other factors that may affect the fragility of intimal capillaries in general are now being investigated.

SUMMARY AND CONCLUSIONS

Two cases of thrombosis of the pulmonary artery and its branches are reported. In each case the various thrombi were attached to the intima at points where hemorrhages into atheromatous plaques had occurred. It would appear that intimal hemorrhage in the pulmonary artery results from the rupture of capillaries which are derived from

the arterial lumen. The rupture of intimal capillaries with intimal hemorrhage should be included in the list of causes of pulmonary artery thrombosis.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH EXPERIMENTAL ALTERATIONS IN BLOOD POTASSIUM IN CATS

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THE increasing interest in electrocardiographic abnormalities which are not due to structural changes in the myocardium has prompted our study of the effect of potassium on the electrocardiogram. An intimate relationship of potassium to automatism and to bioelectric phenomena seems fairly certain, in the light of current knowledge, and numerous investigators have studied the effects of potassium on heart muscle strips, the intact heart, and heart-lung preparations.

Electrocardiograms with concomitant potassium determinations on the intact, unanesthetized subject following potassium administration are rare.

Wiggers[1] produced electrocardiographic changes similar to those due to coronary occlusion by applying with a brush a 20 per cent solution of potassium chloride directly to the ventricle of the dog. Wiggers and his associates[2, 3] described electrocardiographic changes in dogs following intravenous and intracardiac injections of potassium chloride. These changes varied with the amount of potassium chloride injected and with the site and speed of injection. Concentrations of serum potassium were not determined. Harris and Levin[4] noted slowing of the human heart and slight diminution in the height of the P waves following the administration of 5 c.c. of 5 per cent potassium chloride solution. They conclude that there is no relation between electrocardiographic changes and concentration of potassium in the serum, but from the data presented this conclusion does not seem justified.

In five experiments on four dogs, Winkler, Hoff, and Smith[5] found marked changes in the electrocardiogram, with eventual cardiac arrest, following the intravenous administration of 1.12 per cent potassium chloride solution at the rate of 10 c.c. per minute.

In the present study the potassium chloride was given intraperitoneally because Zwemer and Truszkowski[6] had found that this procedure gave more predictable results and smoother blood potassium curves.

MATERIALS AND METHODS

Eight normal cats were prepared for electrocardiographic observation, using the three standard leads. One or two control electrocardiograms were taken, and

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whole blood was obtained for determination of potassium content by the Truszkowski-Zwemer method.[7] Whole blood determinations are permissible in the cat, since the potassium contents of cells and plasma rise and fall together and are not so widely different as in other species.[8] Potassium chloride (10 per cent solution) was then injected intraperitoneally into seven of the animals, and 10 per cent sodium chloride solution into the eighth as a control. Repeated whole blood samplings and electrocardiograms were taken at intervals of from five to fifteen minutes until death or apparent recovery. If death ensued, blood from various vessels (cf. Zwemer and Pike[9]) and fluid from the pericardium and cerebrospinal system were collected for determination of potassium content. The specific gravity of the blood was measured by the falling-drop method of Barbour and Hamilton.[10] Three cats given potassium chloride recovered. One had been given a sublethal dose, another was treated with a large amount of physiologic saline, and the third was injected with eschatin.*

RESULTS

The outstanding results in the individual animals are given below, and the chief effects of potassium on the electrocardiogram are then briefly summarized.

Specific data are given in Tables I and II, and illustrated by Figs. 1 to 5.

1. Cat 3732.—After the administration of 938 mg. of potassium chloride per kg. (in 10 per cent solution) intraperitoneally, the blood potassium content showed a gradual rise from 35.2 to 71 mg. per cent. Electrocardiograms taken at ten-minute intervals showed progressive inversion of the T waves in Leads II and III. These changes were marked; the waves, which had been normally upright, became deeply inverted. When the blood potassium content reached 47.9 mg. per cent (30 minutes after injection), intraventricular block appeared, and the QRS complexes assumed the appearance of those which are typical of bundle branch block. Subsequent records showed a marked increase in the intraventricular block, and what was probably complete auriculoventricular block with auricular asystole or auricular fibrillation. The intraventricular block increased, and the ventricular rate was very slow in the last record obtained before death, seventy minutes after injection.

2. Cat 3734.—After the administration of 963 mg. per kg. of potassium chloride intraperitoneally, in 10 per cent solution, the blood potassium content rose from 22.8 to 90 mg. per cent. Electrocardiograms taken at five- and ten-minute intervals showed, at first, flattening and a tendency to inversion of the T waves in Leads II and III. Partial intraventricular block was first noted when the blood potassium level was approximately 43 mg. per cent. When the blood potassium content rose above 66 mg. per cent, complete auriculoventricular block appeared, with occasional paroxysms of ventricular

*For which we take this opportunity to thank Parke, Davis, and Company.

TABLE I

SUMMARY OF ELECTROCARDIOGRAMS AND BLOOD STUDY PROTOCOLS; EKG CONTROL MEASUREMENTS AND MOST IMPORTANT SUBSEQUENT CHANGES

NO. AND PROCEDURE	RESULT	BLOOD K (MG. %)	BLOOD SP. GR.	RHYTHM	VEN. RATE	P MM.	P-R SEC.	AXIS	QRS DUR.	QRS VOLT	T_1	T_2	T_3
No. 3732 938 mg. KCl/Kg.	death in 70 minutes	control 35.0 maximum 72.0 4 deter.		normal to complete A-V block and aur. fib. or asyst.	252 to 38	2 to 3 to 0.2	.06 to fib.	none to rt.	.04 to .21	6.5 to 10.7 to 15.6	iso. to -.3 to +1.3	+4.1 to -.8 to -13.3	+1.2 to -.5 to -16.2
No. 3734 963 mg. KCl/Kg.	death in 94 minutes	control 23.0 maximum 66.0 death 110.0 11 deter.		normal to aur. asyst. to ven. tachysyst. to ven. fib.	160 to 200 to fib.	1 to 1.5 to -	.09 to .05 to -		.04 to .14	4.2 to 5 to 10+	+.6 to +0.8 to -4	+1 to +1.8 to +6	+1.3 to +2.2 to +8
No. 3743 800 mg. KCl/Kg.	death in a convulsion in 140 min.	control 40.0 maximum 59.2 9 deter.	control 1.049 max. 1.054 later 1.052	normal to inc. A-V block to aur. fib. or standstill	175 to 190 to 44	1.5 to 3 to -	.08 to inc. block	rt. to ?	.03 to .30	8.5 to 6 to 19	iso. to +9	+1.2 to +25	+1.2 to +0.7
No. 3744 600 mg. KCl/Kg.	death in 6 hours and 50 minutes	control 31.8 maximum 90.2 9 deter.	contr. 1.048 max. 1.060	normal to aur. fib. to aur. and ven. stand.	180 to 16	2 to -	.08 to aur. fib.	none	.03 to .12	9 to .12	iso. to -4.5	+1 to -6 to +5	+1 to -7 to +3

TABLE I—CONT'D

No. 3752	apparent	control	19.5	contr.	1.052	normal to partial	180	2	.07	rt.	.03	4	+.5	+2	+2.4
400 mg.	recovery	maximum	34.5	max.	1.059	A-V block to	to	to	to	to	to	to	to	to	to
KCl/Kg.	after 4 hr.	final	20.5	final	1.053	aur. or ven.	260	-	.10	left	.07	10	-3	+8	+10
	15 min.	10 deter.				tach. to normal	to	to	to			to	to	to	to
							170	2	.06			7	iso.	+2	+1.5
No. 3752	nearly re-	control	29.7	contr.	1.053	normal	170	2	.06	none	.03	7	iso.	+2	+1.5
200 mg.	covered	maximum	37.8	max.	1.055		to	to	to	to		to	to	to	to
KCl/Kg.	after 1 hr.	final	28.8	final	1.053		210	3	.08	left		3	+.3	+3	+2.5
	37 min.	6 deter.						to	to	to		to		to	to
								2.5	.06	none		5		+1.5	+1
No. 3755	recovery	control	23.7	contr.	1.053	normal to partial	136	2	.09	none	.04	5.5	iso.	-.8	-.8
600 mg.	after 2 hr.	maximum	49.0	max.	1.061	A-V block, aur.	-70	to	to	to	to	to	to	to	to
KCl/Kg.	45 min.	final	43.7	final	1.059	stand. to ven.	-280	0.7	.14	left	.20	12	-2.3	+6.5	+8
followed		1 week	29.8	1 wk.	1.051	fib. to ven. tach.	to	to	to	to	to	to	to	to	to
by 30 c.c.		later				to aur. stand.	95	2	0.11	none	.04	5	+.5	-.6	-1
adrenal															
cortex															
extract															
No. 3754	almost com-	control	23.3	contr.	1.053	normal to partial	167	1.2	.09	rt.	.03	8	iso.	+2	+1
600 mg.	plete re-	maximum	44.3	max.	1.060	A-V block to	to	to	to	to	to	to	to	to	to
KCl/Kg.	covery in	final	26.9	final	1.042	aur. stand. to	260	3	.11	left	.12	9	-1.0	+5	+6
followed	-2 hr.	17 deter.				A-V block to	to	to	to	to	to	to	to	to	to
by 500						normal	200	1.5	.10	rt.	.03	7	+.6	+1.3	+1
c.c. phys.															
saline															

TABLE II

DETAILED PROTOCOL OF EXPERIMENT ON CAT NO. 3755 (600 MG. KCl/KILO, THEN ADRENAL CORTEX EXTRACT)

TIME AFTER INJECTION	BLOOD K	SP. GRAV. CAP. BLOOD	RHYTHM	RATE	P	P-R	QRS DUR.	AXIS DEV.	QRS I	QRS II	QRS III	T_1	T_2	T_3	REMARKS
Control	23.7	1.0526	Tach.	136	2.0	.09	.04	No	+1 -.5	+4.7	+5.5	0	-.8	-.8	28 c.c. 10% KCl injected intraperitoneally.
-KCl 10 min.		1.0569	Tach.	134	2.0	.09	.05	No	+1.2 +.4	+4	+4.2	0	-1	-.8	
15 min.	34.5	1.0581													
25 min.			Partial A-V bl. Slower	105	1.0	.14	.09	No	+3.5	+12	+9 to +7	-1.7	-4	+.6 -4.0	Prolonged A-V and intraventricular conduction. Marked changes.
30 min.	43.4	1.0583													
35′	42.8	1.0578													Left bundle branch block now present, with wide QRS, coupling, and questionable ventricular fibrillation. Marked increase in abnormalities.
40′			Complete aur. standstill ? V. fib.	75			.16	Lt.	+2.5	-6	-7	-1.5	+6.5	+8	
42′			Aur. standstill Runs of ? V. tach.	170 to 120 to 100			.12 .16	Lt.	+3	+1 -3	-10	-2	+4.5	+8	Lead III shows wider QRS with more rapid rates.
50′	45.5	1.0583													
55′		1.0613													Sinus rhythm has appeared again and bundle branch block is less marked. Marked improvement.
57′			Tach.	115	.7	.09	.14	Lt.	3.3	-3	+1 -8	-2.3	+5	+7	
30′	45.4	1.0601 (h)													Intracardiac injection 10 c.c. eschatin.
1°3′	(h)		V. fib. V. tach.	220			?.16	Lt.?		?-3	?-6		?+4.5	?+2	Ventricular fibrillation. Marked increase in EKG abnormalities.
1°5′															10 c.c. eschatin intramuscularly.

TABLE II—CONT'D

1°8′	46.8														
1°10′			V. tach. or V. fib.	290			?.20								Borderline vent. fibril. or vent. tach., with even more rapid rate. EKG suggests dying heart.
1°19′	44.7	1.0603													
1°31′			Aur. stand-still	140 to 180			.20 + or −	Lt.	+3	?-5	?-10	-2	?+6	?+5.5	Bizarre complexes variable in size, shape, rhythm, and rhythmicity, suggesting dying heart.
1°55′	45.8	1.0585													
2°			Aur. stand-still	120			Var. R.	Lt.		Vari-able			Vari-able		Complexes vary with rate, showing high-grade bundle branch block due to shorter rest periods. Coupling occasionally present.
2°5′	43.7 (h) 49.0	1.0594 (h)													Cell volume 43.4. Plasma sp. grav. 1.0312. Plasma protein 8.25%. Intracardiac injection 10 c.c. eschatin.
2°9′			Vent. tach.	230			.14	Lt.	?+3.5	?+6	?-8	?-2.5	?-4.3	?+6	Vent. tach. with shorter QRS and regular rhythm. Slight improvement in EKG.
2°20′			?able S.A. Tach.	280	?2.6	.06	?-7	Lt.	up	+4.2	?-3 +1	in-vert-ed	-1.5	1?	Sinus tach. probably present, with shorter QRS duration but rapid rate. In subsequent record P waves were absent and QRS much wider.
2°24′	43.7	1.0595													
2°35′			? Aur. stand-still	160			.09	No	+3.2	+8	+5.5	2	-4	+2 -1.5	Slower rate, absence of P waves, shorter QRS duration and clearing of axis deviation. Improved.
2°40′	48.7 (s)	1.0586													Cell volume 41.6. Plasma sp. grav. 1.0296. Plasma pro. 7.7%.
2°45′	29.8	1.0515													
1 week later			Bradycardia	95	2	.11	.04	No	+1.5 -0.7	+5	+.5	+.5	+.5 -.6	+.5 -1	EKG similar, but not identical to, initial record.

tachycardia. Ventricular fibrillation appeared ninety minutes after injection and was followed by death.

3. Cat 3743.—The animal died in a convulsion two hours and twenty minutes after an intraperitoneal injection of 800 mg. per kilo. Gradual increases in the blood potassium level were accompanied by intraventricular block, followed by auriculoventricular block with what was probably auricular flutter.

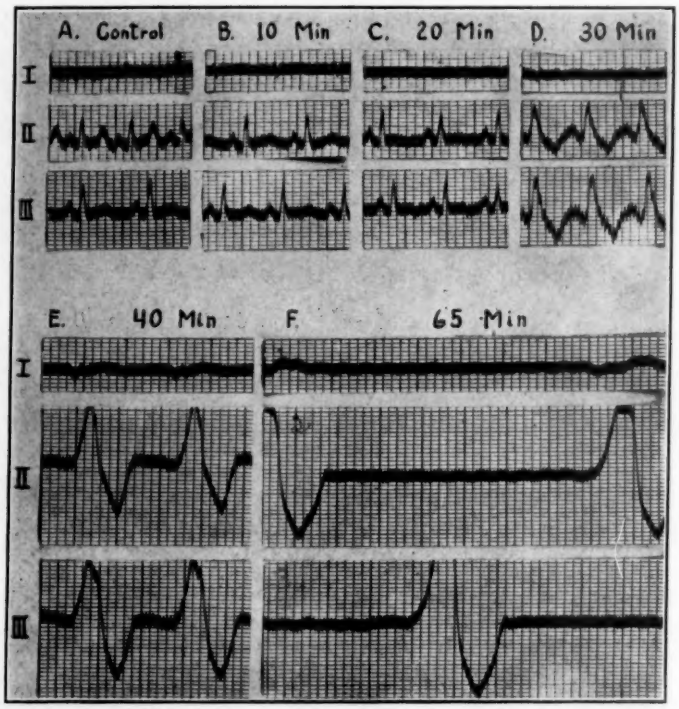

Fig. 1.—Cat 3732. Records taken before and after intraperitoneal injection of 938 mg. of potassium chloride per kilo in 10 per cent solution show progressive inversion of T waves in Leads I and II, followed by intraventricular block and either auricular standstill or auricular fibrillation with complete auriculoventricular block. The tracings were taken with standard technique. The fine vertical lines fall every .04 second, and the fine horizontal lines represent a string deflection of 0.1 millivolt. Blood potassium levels were: control, 35.2 mg. per cent; 47.9 mg. per cent at 30 minutes; 71.2 mg. per cent at 55 minutes. At death, the serum potassium was 72.2 mg. per cent.

4. Cat 3744.—Progressively increasing intraventricular block, auricular fibrillation, and, finally, auricular and ventricular standstill were observed over a period of six hours and fifty minutes following the intraperitoneal injection of 600 mg. per kg. of potassium chloride solution. The electrocardiographic abnormalities increased in spite of a slight decrease in the blood potassium level after the first ninety minutes.

5. Cat 3752.—Sublethal doses of potassium chloride produced transient electrocardiographic changes. Injection of 400 mg. per kg.

produced intraventricular and auriculoventricular block and ventricular tachycardia, with a return to normal four hours and fifteen minutes after injection. Immediately after recovery, a second injection of 200 mg. per kilo caused a rise of 8.1 mg. per cent in the blood potassium level, which was associated with partial auriculoventricular block and minor T-wave variations.

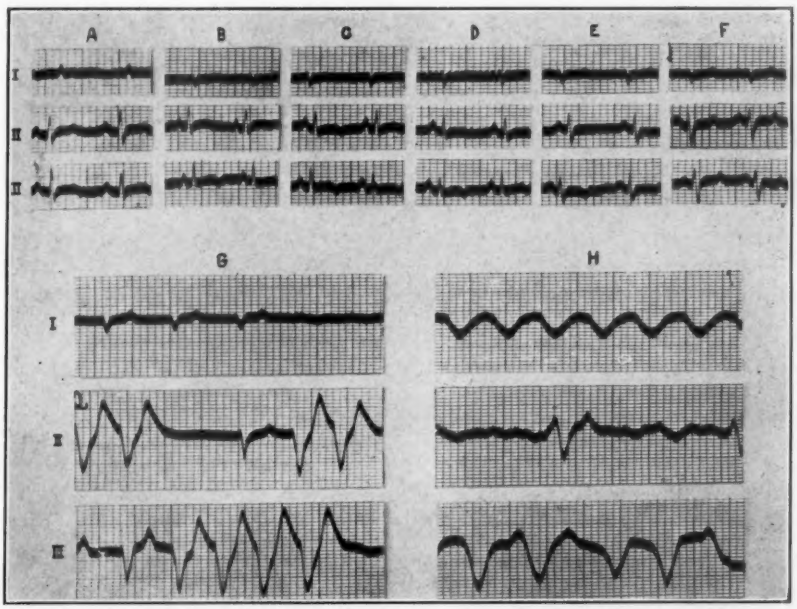

Fig. 2.—Cat 3734. After the intraperitoneal injection of 963 mg. of potassium chloride solution per kilo, tracings show T-wave changes, followed by intraventricular block, auricular standstill, irregular ventricular tachysystole, and ventricular fibrillation. A to H show control and tracings taken at 10, 20, 30, 50, 70, 80, and 90 minutes. Approximate potassium values for tracings A to F were: 22.8, 28.5, 35.8, 35.2, 43, and 59.6 mg. per cent.

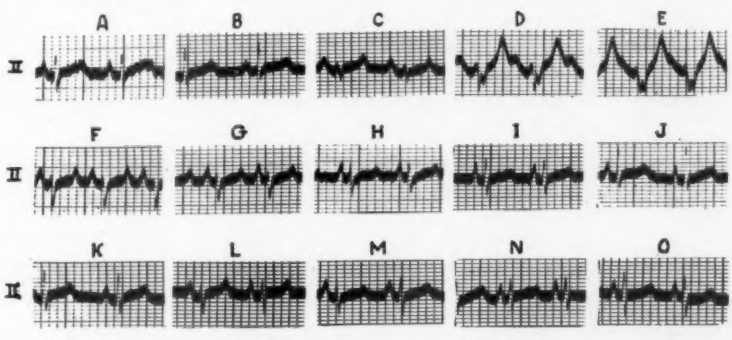

Fig. 3.—Cat 3752. Only Lead II is shown. After injection of 400 mg. of potassium chloride solution per kilo, tracings A to E show the development of partial auriculoventricular and intraventricular block, followed by return to normal. Subsequently, a smaller dose (200 mg. per kilo) caused only slight changes in rate, voltage, and P-R interval, again followed by return to normal (J to O). Timing of tracings A to O is as follows: control, 5, 25, 40, 60, 90, 115, 130, and 230 minutes; second control (J), 15, 30, 45, 60, and 90 minutes. Approximate corresponding potassium levels, in order, are: 19.5, 23.6, 30.7, 32.9, 34.5, 34.0, 30.0, 27.4, 20.5, 29.7, 37.8, 33.0, 33.7, 34.4, and 30.3 mg. per cent.

6. Cat 3755.—Injection of 600 mg. per kg. of potassium chloride solution caused intraventricular and partial auriculoventricular block, followed by complete auricular standstill and periods of ventricular fibrillation, tachycardia, and tachysystole. Recovery followed intramuscular injection of 10 c.c., and intracardiac injections of 20 c.c., of adrenal cortical extract (Parke, Davis, and Company).

7. Cat 3754.—After the appearance of auriculoventricular and intraventricular block caused by injecting 600 mg. of potassium chloride solution per kg., 500 c.c. of physiologic saline were administered intraperitoneally. This was followed by a return almost to normal of both the blood potassium level and the electrocardiogram in less than two hours after the potassium chloride had been injected.

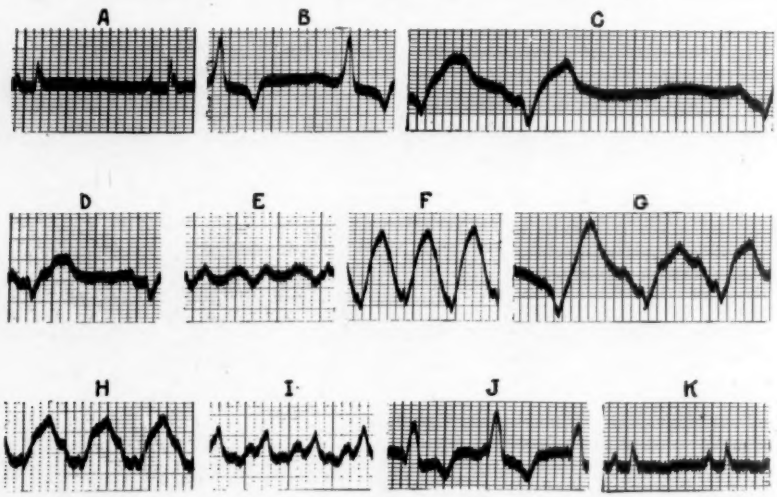

Fig. 4.—Cat 3755. Only Lead II is shown. After administration of 600 mg. of potassium chloride solution per kilo, intraventricular block, partial auriculoventricular block, ventricular tachycardia, irregular ventricular tachysystole, auricular standstill, and the final return to normal are shown. This animal received 10 c.c. of eschatin one hour after the potassium chloride injection, and another 10 c.c. sixty-five minutes later, but with questionable benefit. The tracings, in order, show control, 25, 40, 57, 63, 70, 91, 129, 140, 155 minutes, and 1 week after potassium chloride. The approximate corresponding blood potassium levels are 23.7, 40.4, 44.1, 45.4, 46.0, 45.1, 48.0, 44.6, 43.7, and 29.8 mg. per cent.

8. Cat S-7.—As a control, 27 c.c. of 10 per cent sodium chloride solution (600 mg. per kg.) were injected intraperitoneally. Records taken at half-hour intervals showed no change other than a slight acceleration in rate. The blood potassium level stayed practically constant, varying only between 21.7 and 20.7 mg. per cent.

The relation of potassium administration to changes in the electrocardiogram may be summarized as follows:

Heart Rate.—The effect on the rate was inconstant before A-V block (slowing), or ventricular tachycardia, or sinoauricular tachycardia appeared. Early variations in rate could have been caused by nervous excitement.

P Waves.—The P waves decreased in amplitude by about 1 mm., in two instances, before they disappeared. They disappeared in all cases in which the cat received 600 mg., or more, of potassium chloride per kg. The blood potassium level at the time of the disappearance of the P waves and appearance of auricular standstill was quite variable, ranging from 36.4 to 90.2 mg. per cent.

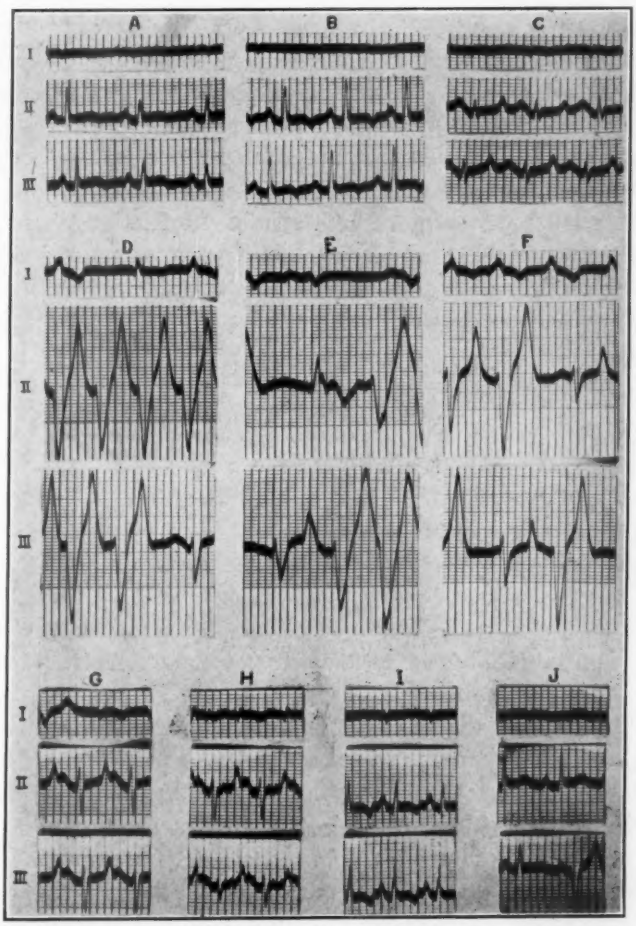

Fig. 5.—Cat 3754. Tracings A to F show reversal of T waves and development of intraventricular and partial auriculoventricular block and ventricular tachysystole after injection of 600 mg. of potassium chloride solution per kilo. Fifty minutes after the potassium chloride administration, an intraperitoneal infusion of 500 c.c. of physiologic saline was started. Tracings F to I show a fairly rapid subsequent recovery. In order, the records show: control, 8, 20, 30, 45, 63, 80, 94, and 110 minutes, and J, 1 week after potassium chloride. The approximate corresponding blood potassium levels are: 23.9, 31.0, 35.5, 36.4, 40.2, 93.3, 37.0, 36.1, 33.1, and 26.9 mg. per 100 ml.

P-R Interval.—Partial A-V block occurred in all the experiments. It was first observed when the blood potassium level ranged from approximately 30.7 to 66 mg. per cent, with an average of about 45 mg. per cent. In the four recovery experiments it disappeared at varying levels, either higher or lower than that at which it was first observed.

QRS Complexes.—The voltage of QRS became lower in three experiments and higher in two, in the early stages of poisoning before intraventricular block appeared. The blood potassium content at the time of the changes in voltage ranged from 30.7 to approximately 44 mg. per cent. Intraventricular block was observed in all the experiments, appearing with a blood potassium range of approximately 31 to 55 mg. per cent, averaging about 42 mg. per cent.

T Waves.—Flattening or inversion of the T waves (especially in Leads II and III) occurred in four experiments before the appearance of intraventricular block. In these animals the blood potassium ranged from 28.5 to approximately 44 mg. per cent, with an average of about 36 mg. per cent. Marked T-wave changes eventually occurred, as would be expected with the appearance of intraventricular block. Ventricular standstill, or so-called ventricular fibrillation,[4] was observed in four experiments, the blood potassium ranging from 55.3 to 109.7 mg. per cent. Ventricular tachysystole was observed in four experiments, with blood potassium levels varying from 40.2 to approximately 57 mg. per cent.

COMMENT

Our results confirm the findings of Wiggers[11] and Winkler, et al.,[5] in respect to the abnormalities in the electrocardiogram following potassium administration. They extend the observation that many of the changes may be reversed.

The sequence of the various electrocardiographic abnormalities is fairly uniform in each experiment, as are the potassium changes. However, the relative elevation of blood potassium above the control level showed a less close relationship to the electrocardiographic changes in the different experiments than did the actual blood potassium level. Neither the dosage of potassium chloride nor the rapidity with which electrocardiographic changes occurred seemed to be exactly related to the potassium level at which the changes took place.

The similarities between the abnormalities shown in our electrocardiograms and those produced in muscle-strip preparations in which the potassium content of the perfusion fluid was the only variable[12 a, b, c, d, e] suggest that our electrocardiographic changes may well have been due chiefly to hyperpotassemia. The actual responsibility of potassium for the changes in the electrocardiograms can only be estimated, with our present knowledge, since changes in the concentration of other ions during hyperpotassemia may play an important part. Blood concentration per se is probably not important, as we found no relationship between blood specific gravity and electrocardiographic changes in five of our experiments.

The blood potassium levels reported in the present experiments are not purely of pharmacologic interest, since equally high levels have been

found in cats after the experimental production of intestinal obstruction,[13] intestinal fistulae,[14] shock,[15] and adrenal insufficiency.[16 a, b, c] In the last-named syndrome, Nicholson and Soffer[17] noted slowing of the heart rate and auricular fibrillation in eight adrenalectomized dogs whose blood potassium levels were elevated. In two of the animals, normal rhythm was restored after the administration of 200 c.c. of physiologic salt solution.

In certain clinical conditions, changes in the electrocardiogram may be occasioned by potassium release from damaged cells, especially if the general condition of the individual be poor. Unpublished observations by Chamberlain, and a report of a case of intestinal obstruction by Scudder, Zwemer, and Whipple[18] would indicate that this is true.

Addendum

Since this paper was written, two papers have appeared calling attention to changes in the electrocardiogram in adrenal insufficiency concomitant with elevations in serum potassium. Hall, G. E., and Cleghorn, R. A.: Cardiac Lesions in Adrenal Insufficiency, C. M. A. J. **39**: 126, 1938. Thompson, W. A. R.: Potassium and the T Wave of the Electrocardiogram, Lancet **1**: 808, 1939.

CONCLUSIONS

1. Experimental increases in the blood potassium content in the cat are associated with abnormalities in the electrocardiogram.

2. In order of appearance, the usual changes are: lowering or inversion of T waves, decrease or increase of QRS voltage, auriculoventricular and intraventricular block, auricular standstill or auricular fibrillation, ventricular tachycardia or tachysystole, ventricular fibrillation, and ventricular standstill.

3. The electrocardiographic abnormalities are reversible, and parallel roughly the return of the blood potassium content to normal when a sublethal dose is given, or following the administration of physiologic saline or adrenal cortex extract.

4. The potassium levels at the time electrocardiographic changes appear vary in different cats. This suggests that factors other than blood potassium may also be important.

5. Potassium administration produces marked abnormalities in the electrocardiogram when the blood potassium content is considerably below the level reached in experimental adrenal insufficiency, intestinal obstruction, or intestinal fistula.

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RUPTURED POPLITEAL ANEURYSM

Report of Four Cases

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NEXT to the arch of the aorta, the popliteal artery is the vessel most commonly the site of aneurysm. In contradistinction to the aorta, it is readily accessible to surgical treatment. Syphilis and arteriosclerosis are the common etiologic agents of the nontraumatic variety of aneurysm. Trauma or strain may cause aneurysm due to either agent to rupture. The factor precipitating the rupture may have been so trivial as to have been unrecognized or forgotten. The rupture may thus appear to have been spontaneous, as with aneurysm of the aorta. The popliteal artery is situated at a point where it is subjected repeatedly to severe strain, especially in laborers. This fact probably accounts for the predilection of aneurysm for this artery, and for the frequent ruptures. When rupture, either of a pathologically weakened artery or of a normal one, occurs as the result of a penetrating wound, a false aneurysm forms. This consists of a blood clot without walls other than the surrounding muscles and fascia. The four cases to be reported illustrate many of the important points in the diagnosis, and how the circulation becomes re-established, when rupture of a peripheral artery, such as the popliteal, occurs.

REPORT OF CASES

Case 1.—This case was first reported in 1936. The patient, M. M., a negro laborer, aged 49 years, entered Gallinger Municipal Hospital for the first time on June 20, 1935, complaining of pain and swelling of the right leg. About one month previously this leg had been struck behind the knee by a falling tub. Prior to that time he had not been aware of any trouble in the leg. The injury did not disturb him much at the time, but fairly rapidly a swelling developed in the popliteal fossa and became moderately painful. In a few days the whole leg became swollen and painful. The swelling subsided gradually to about half of its maximum. The patient had had a penile lesion at the age of 16 years and gonorrheal urethritis later, and two years before he had been told that he had high blood pressure. Physical examination revealed, besides the changes in the leg, some dental caries, a few subcrepitant râles at the bases of the lungs, more than moderate enlargement of the heart, a loud systolic precordial murmur, and a blood pressure of 150/100. In the right popliteal region there was a slightly expansile tumor which projected about 5 cm. posteriorly. It was firm and immovable, and a soft systolic murmur was audible directly over it. The foot and ankle were moderately edematous. The Kahn test

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on the blood was negative on three occasions. Other laboratory tests showed nothing abnormal. Hospitalization lasted three weeks. The temperature and pulse rate were normal, and the condition of the right leg did not change. The patient refused operation and returned home. The diagnosis was aneurysm of the right popliteal artery.

He returned Oct. 21, 1935. The whole right leg, below the middle of the thigh, had become much larger, was semiflexed at the knee, and could not be straightened. Walking was impossible. The greatest swelling was in the popliteal space. Here there was a small fluctuant area. A small needle was inserted in this region, and blood was easily aspirated. The systolic bruit was still audible. The leg felt warmer than the unaffected one. The mouth temperature was elevated less than a degree. Examination of the blood and other laboratory procedures showed nothing abnormal, including again the Kahn test on the blood. A roentgenogram of the chest revealed a somewhat dilated and tortuous aorta and that the heart was moderately enlarged and of the "aortic type."

Arteriograms were made by means of thorium dioxide sol (Thorotrast Heyden). They showed that the femoral artery faded out just above the popliteal fossa. Just behind the knee joint there was a semilunar space filled with the contrast medium. This appeared to be peripherally located in the middle of a large, soft-tissue tumor. Some distance below this both the anterior and posterior tibial arteries were visible, together with some small branches.

On another day, thorium dioxide was injected into the femoral vein in a similar manner, and roentgenograms were made. As the vein passed the popliteal mass it appeared to be compressed peripherally, and below the mass it could not be followed very far. Some of the contrast medium previously injected still remained in the tumor.

The case was considered to be one of a popliteal aneurysm too large to be treated except by amputation of the extremity. Consequently, on November 2, amputation was performed at the middle of the thigh. The postoperative course was uneventful, and the patient left the hospital on December 15 with the stump thoroughly healed.

The amputated extremity was carefully dissected to isolate the vessels and the aneurysm (Fig. 1). The popliteal artery and vein were followed distally. They appeared to be normal. A short distance above the knee joint the continuity of the artery apparently ceased. Just below this point a large, dark blood clot, measuring about 10 by 8 by 8 cm., had formed and pushed the muscles posteriorly. The muscles were infiltrated with blood. After further dissection it was observed that there was a false sac about the clot, composed of a layer of compressed coagulum, and that on one side there was a broad ribbon of fibrous tissue with a smooth inner surface. The latter was continuous with the popliteal artery, and about 5 cm. below the apparent end of this artery a lumen was found in the fibrous wall which was undoubtedly the lower orifice of the popliteal artery in the wall of a ruptured aneurysm. A hollow probe was inserted through this lumen and passed down the remaining 7 cm. of the popliteal artery into the anterior tibial artery. The branching of the popliteal artery occurred about 2 cm. below the aneurysmal sac. The popliteal vein was compressed by the side of the artery external to the aneurysmal sac.

Microscopic sections were made through the popliteal artery and through various parts of the wall of the ruptured aneurysmal sac, including one across the lower portion of the popliteal artery and vein. These did not reveal any definite evidence of syphilis. The popliteal artery was only moderately atherosclerotic. The wall of the aneurysm was composed of hyaline connective tissue, and sections stained with acid orcein showed interrupted narrow bands of fragmented elastic tissue nearer the inner surface of the wall of the sac. The section

through the lower portion of the popliteal artery and vein showed moderate atherosclerosis of these vessels. The artery lay just within the wall of the sac, the vein just lateral to it.

The patient was seen again in the Outpatient Department in January, 1936. The stump was in good condition, but the patient was not feeling well. A large, reniform mass was palpated in the right flank. He entered the hospital three weeks later, but before a definite diagnosis could be made he died of some cerebral complication.

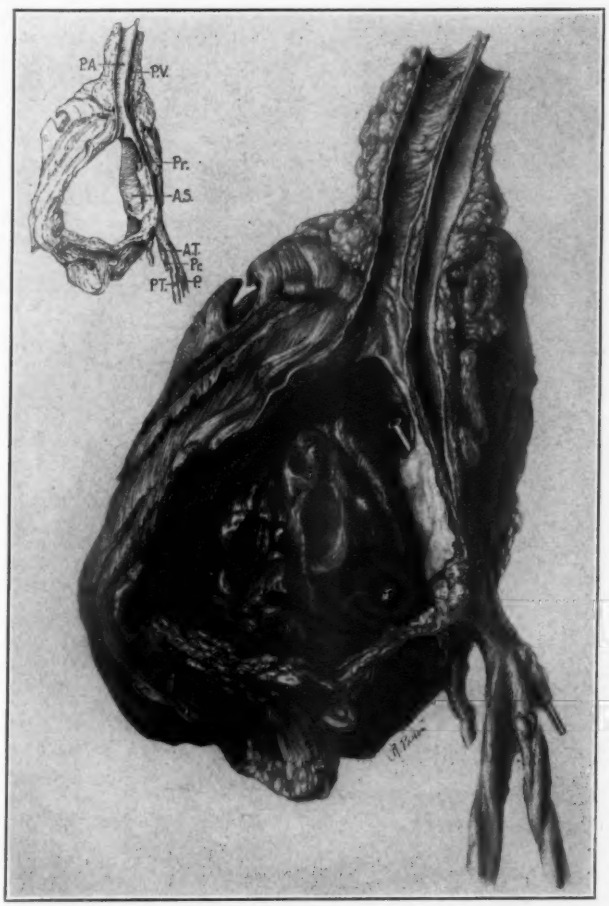

Fig. 1, Case 1.—The ruptured aneurysm, dissected after amputation.

CASE 2.—J. M., a colored man who gave his age as 56 years, but who looked 10 years older, entered Gallinger Municipal Hospital Dec. 11, 1937, because of enlargement of the left leg below the knee. The leg had begun to disturb him just one year before, with a little pain and swelling of the left foot and a sensation as of pins and needles. He rubbed his leg and soaked his foot, but continued to work. The calf began to swell, and by June, 1937, it was quite large. Pain occurred intermittently, usually after eating meat, according to the patient. The swelling finally became so great as to make walking impossible. The only traumata to the leg had been a blow in 1917, and a fall early in 1936. He had had a penile lesion three years before.

Examination showed nothing of importance except a tremendous, fusiform, smooth, stony-hard swelling of the left calf (Fig. 2). This leg was several times larger than the other. The foot was moderately edematous, and the popliteal artery and vessels in the foot could not be felt to pulsate, apparently because of the edema. The skin was dry, roughened, and thick. Roentgenograms showed marked periosteal proliferation of the upper half of the tibia. Arteriograms were unsatisfactory. The blood Kahn reaction was moderately positive (2 plus).

Amputation was performed in the lower third of the thigh, and the patient's recovery was essentially uneventful. Dissection of the specimen showed that the swelling consisted of a tremendous blood clot, in the upper part of which the posterior tibial artery was found to terminate in a dilated portion which was continuous with a false sheath over the clot. The vessel was found again about 15 centimeters lower down. The anterior tibial artery was traced through the edge of the clot. Microscopic sections through the posterior tibial artery showed extensive degenerative changes of a nonspecific nature through the entire wall, and a little thickening of the intima.

Fig. 2, Case 2.—Tremendous enlargement of left calf.

The surgeons had considered that this was probably a case of sarcoma. Arteriograms would have enabled us to make a correct diagnosis. As a matter of fact, ruptured aneurysm was thought of, but was not considered seriously because of the stony hardness of the tumor. However, the shape of the enlargement was more consistent with this diagnosis. It is astounding that there were no serious trophic changes in the extremity caused by compression of the arteries, and only moderate edema from compression of the veins.

CASE 3.—F. B., a negro laborer 35 years of age, entered Georgetown University Hospital Feb. 15, 1938, because of a painful swelling in the left popliteal region. For about five months before admission the left leg and foot had been moderately swollen. The swelling practically disappeared each night. About five weeks before admission a moderately painful "lump" appeared in the left popliteal region. The patient claimed that at first he was able to rub this localized swelling away, but for two weeks it had been growing larger. There was no history of injury of any kind. He had had a penile chancre seven years before, for which a course of treatment had been received at that time.

Physical examination showed nothing important except a rounded, somewhat tender, fluctuant, firm, pulsating mass in the lower part of the left popliteal region, about the size of a large lemon. A systolic thrill and bruit were present directly over the mass. Arterial blood was aspirated from it. Just proximal to the mass there were two, small, tender nodules that felt like enlarged, inflamed lymph nodes. There was slight edema of the leg and foot. Arterial blood pressure measurements on various occasions showed relatively little difference between the two thighs. The pulsations of the left dorsalis pedis artery were very feeble, and those of the posterior tibial artery could not be felt. There were no trophic changes, and the left leg felt warmer than the right, especially over the mass. The blood Wassermann and Kahn reactions were strongly positive (4 plus).

Fig. 3.

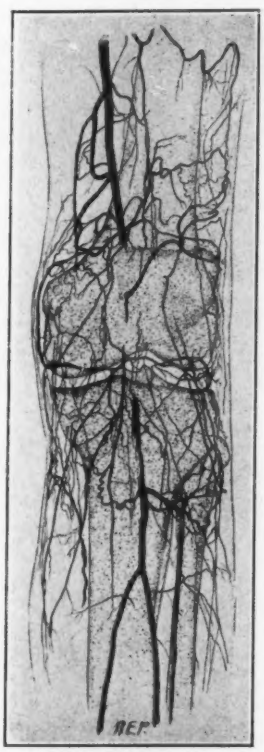

Fig. 4.

Fig. 3, Case 3.—Preoperative arteriogram.
Fig. 4, Case 3.—Exact line drawing of arteriogram made five weeks after operation.

Arteriograms made by means of thorotrast showed, in the first film, narrowing of the shadow of the left popliteal artery to a point (Fig. 3), and, in a second film, the presence of a little thorotrast in the anterior tibial artery above the ankle. These findings were interpreted as evidence of rupture of a small popliteal aneurysm.

Three weeks were utilized in preparation for operation. This consisted in intramuscular injections of bismuth subsalicylate (four in all), the oral administration of saturated solution of potassium iodide, and compression of the left femoral artery against the pubic bone two or three times daily for periods pro-

gressing from ten minutes to one-half hour. During this time the mass became a little larger and firmer, and its pulsations feebler. Blood which was aspirated was darker than originally, but was under good pressure. The oral temperature was normal except on two days, when it rose to 100° F.

On March 19, 1938, operation was performed by Dr. Fred Sanderson. An incision was made over the mass and a false sac exposed. The popliteal vessels were found to be displaced medially. These vessels were isolated and ligated proximal to the mass, after which the mass was incised and found to be a large blood clot, which was removed. It was not considered advisable to attempt to dissect the popliteal artery in order to find the point of rupture, but a portion of the artery distal to the point of ligation was removed, and the incision was closed. Recovery was entirely uneventful. The patient left the hospital just two weeks after the operation.

Fig. 5, Case 3.—Cross section of excised portion of popliteal artery, magnified 36 times.

Within a few days pulsations were found to be stronger in the left dorsalis pedis artery and were again felt in the posterior tibial artery. Five weeks after the operation other arteriograms were made. These showed that a remarkable collateral circulation had been established, bridging the gap in the popliteal artery and maintaining blood flow through the main arterial pathways (Fig. 4). In the distal part of the popliteal artery there was an eccentrically narrowed portion which probably indicated localized disease of the vessel.

Microscopic sections of the excised portion of the popliteal artery showed extensive fibrous replacement of the media (Fig. 5). On one side of the wall

there was very little muscle left; on the other side there was destruction of about 50 per cent of the muscle. The greater part of the lumen was filled by light, fibrous, in general sparsely cellular tissue containing practically no blood vessels. This tissue had apparently resulted mainly from proliferation of the intima, rather than from thrombosis within the lumen, although there was a thrombus intimately associated with the free margin. The internal elastic

Fig. 6, Case 4.

Fig. 7, Case 4.—Preoperative arteriogram.

lamina, as stained with acid orcein, was seen to be somewhat disrupted, but to be present around the vessel in a relatively normal position. The adventitia had been stripped from the vessel. There was no evidence of any active inflammatory process in any part of the vessel wall.

CASE 4.—E. J., a negro laborer, aged 37 years, entered Gallinger Municipal Hospital April 18, 1938, because of a painful swelling behind the right knee.

This was first noticed about Jan. 1, 1938, and had gradually become larger until it had attained the size of an orange. He felt it throb with each beat of the heart. The leg could not be extended completely. He had gone to the outpatient clinic of another hospital because of the swelling, and had been given five injections "for his blood" without apparent effect. He had had a penile lesion 15 years before, and had received five injections at that time. Approximately at the same time he had been cut on the medial aspect of the right knee with a crosscut saw, but recovered promptly, and the scar was now well above the knee and in no relation to the swelling. No other injury had been sustained.

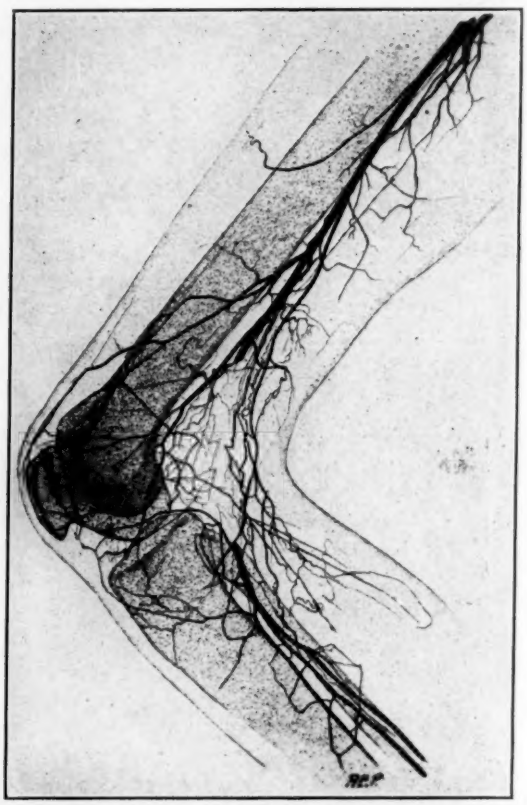

Fig. 8. Case 4.—Exact line drawing of arteriogram made three weeks after operation.

Physical examination showed nothing of interest except for the right leg. A rounded, pulsating mass was present in the popliteal space (Fig. 6), over which a systolic murmur was audible. There were no trophic changes and no edema. The dorsalis pedis and posterior tibial vessels were pulsating feebly. The blood Kahn reaction was strongly positive (4 plus). Arteriograms showed definitely that the popliteal artery had ruptured (Fig. 7). It came to a point in the upper part of the popliteal space; directly behind the knee joint there was a jagged opacity caused by escape of thorotrast, but adjacent to this the popliteal artery was visible again. A fair number of small collateral arteries were present.

Antisyphilitic treatment and intermittent occlusion of the femoral artery were instituted in preparation for operation. An irregular fever of 1° to 2° F. occurred almost daily. The swelling became larger and more painful, and the leg became somewhat edematous.

Operation was performed on May 3, 1938, by Dr. Charles S. White. A large clot was removed from the popliteal fossa, after which the artery was exposed. A small, ruptured aneurysm, less than 2 cm. in diameter, was found. This was resected.

Unfortunately, after the operation there was evidence that the popliteal nerve had been injured, although care had been exercised to avoid it. In a few days dry gangrene appeared in the first and fifth toes. The patient's temperature was normal for three weeks, but the wound became infected and the temperature rose to 103° and 104° F. On June 21 the leg was amputated in the middle of the thigh. The temperature gradually returned to normal, and the stump healed.

Fig. 9, Case 4.—Longitudinal section of the ruptured aneurysm, stained for elastic fibers with acid orcein.

Before the amputation, three weeks after the first operation, arteriograms were again made (Fig. 8). These showed a most remarkable bridging of the resected section of popliteal artery by collateral arteries, so that the function of the popliteal artery was maintained below the knee.

Microscopic sections were made transversely through the popliteal artery and vein just proximal to the ruptured portion, and longitudinally through the artery. The sections were stained with Masson's trichrome. The intima and subintima of the artery were greatly thickened, mainly by a loose, areolar

type of connective tissue containing fibroblasts; in some places this tissue had changed into a dense hyaline substance. The internal elastic lamina was moderately fragmented, but, as a rule, could be traced (Fig. 9). The muscle fibers of the media were separated moderately by fibrous tissue, and in some portions there was considerable infiltration of the media by lymphocytes. The adventitia was composed of dense fibrous tissue containing a few lymphocytes. The popliteal vein was affected in the same way as the artery, but even more so. Its lumen was filled with a clot which was undergoing organization along one side. Two, smaller, medium-sized vessels nearby were so changed as to make it almost impossible to tell whether they were arteries or veins, but one was evidently a branch of the popliteal artery, and the other was probably a vein. Their lumens were practically occluded by subintimal thickening, and their muscular coats were greatly disrupted. The connective tissue between and around the vessels was dense fibrous tissue containing scattered lymphocytes, most numerous in the vicinity of arterioles. In some areas there were considerable collections of erythrocytes. Close to the artery there was a collection of lymphocytes and plasma cells suggestive of a gumma, but nowhere was there the typical perivascular lymphocytic infiltration of the small vessels such as one sees usually in syphilitic vascular disease. As the aneurysm was approached from either direction, the artery became more abnormal, its media being almost entirely replaced by fibrous tissue. The wall of the aneurysm itself was composed of fibrous tissue. Some strands of elastic tissue were imbedded in the wall and constituted the only evidence that this had once been the wall of an artery. These elastic tissue strands were more or less continuous with the internal and external elastic lamina of the artery.

DISCUSSION

The diagnosis of popliteal aneurysm itself is usually not difficult. The presence of a rounded, pulsating, fluctuant mass, with a localized systolic bruit, is always suggestive. In every doubtful case a medium-sized aspirating needle should be inserted to ascertain the nature of the contents of the mass. The diagnosis of rupture of a popliteal aneurysm may not be so easy. When there is a history of a rather rapidly growing swelling, with or without a previous injury, this condition should be thought of. The mass may or may not pulsate. Insertion of an aspirating needle often, but not always, allows the withdrawal of blood or bloody serum. The vessels in the foot often cannot be felt to pulsate. In long-standing cases, such as Case 2, particularly, when the mass has grown large and hard, the diagnosis is most difficult. In doubtful cases arteriography should settle the point. The arterial shadow will end at the site of rupture, and an opacity in the soft tissues will often be seen, indicating escape of contrast medium from the artery. There may be shadows of the tibial arteries at a lower point. In cases of simple aneurysm, arteriograms show no break in continuity and no seepage, although two, or even three, serial films may be necessary to show that blood is flowing through the aneurysm.

Although it may be advisable to try to promote the development of a collateral circulation prior to operation, it is probably wrong to de-

lay operation if the mass is painful and growing rapidly. Apparently, all that is necessary is to remove the clot and to ligate the artery and vein proximal to the point of rupture. Whether a section of the artery should be excised is questionable. In general, the less that is attempted the better the outcome. In Case 3 this procedure was followed, with excellent results. In Case 4 the aneurysm was removed with considerable difficulty, and the nerve was accidentally injured. It is not necessary to ligate the vessel distal to the point of rupture. The question of the advisability of trying to save the limb when the mass has attained a large size and become hard may be raised. Unfortunately, this was not done in Cases 1 and 2. There does not seem to be any reason, however, why the attempt should not be made. If there are no serious trophic changes, there is apparently no way of predicting the outcome.

Of particular interest is the subject of establishment of a collateral circulation. In Cases 1 and 4 the main arteries below the site of rupture were definitely functioning before the operation, as shown by the arteriograms. The question is whether the blood reached these vessels entirely or largely by means of collaterals, or whether it seeped around or through the hematoma to enter the open arteries below. The latter may be the case, since it took longer for the contrast medium to appear in the distal arteries than it should have if it had reached them by collaterals. It is possible, however, that the pressure of the hematoma on small collateral vessels may have slowed the passage of blood through them. In Cases 3 and 4, in which arteriograms were again made, five and three weeks after operation, respectively, there was remarkable bridging of the popliteal arterial defect by numerous collateral vessels, so that the functional integrity of the large artery was maintained. At this time, however, the thorotrast entered the distal part of the artery rapidly, apparently as quickly as if the vessel had been uninterrupted. This method of bridging of defects of large arteries is probably a common one.[1] Apparently, the prevalent idea that a clot usually forms in an artery distal to an area of occlusion is incorrect. Often the vessels remain open and continue to function because of the collateral channels.

Pathologically, the lesions in all four cases were nonspecific. All four men had had chancres, and the serologic tests for syphilis were still positive in three. This fact does not prove that the arterial lesions were of a syphilitic nature. However, in view of all the circumstances, it appears probable that the degenerative changes were the result of syphilitic arteritis. It may be that syphilis can produce lesions of arteries other than those usually described as syphilitic.

Definite trauma had occurred in only one of the four cases. This, a blow on the popliteal fossa, appeared to be the cause of the rupture. In the other cases the rupture was apparently spontaneous.

SUMMARY AND CONCLUSIONS

The popliteal artery is a relatively frequent site for aneurysm. Because of their location, rupture of such aneurysms is comparatively common. This occurs as the result of trivial or unnoticed trauma.

Ruptured popliteal aneurysm should be suspected in any case of progressive and, especially, pulsatile swelling in the popliteal region. Aspiration aids in the diagnosis, but arteriograms are necessary in doubtful cases.

In the four cases reported, pathologic study revealed severe degenerative changes of a nonspecific nature in the artery. All of the patients had syphilis.

REFERENCE

1. Yater, W. M.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, Am. J. Med. Sc. 104: 372, 1937.

LOUD, MUSICAL, DIASTOLIC MURMURS OF AORTIC INSUFFICIENCY

Clinical and Pathologic Observations Upon Their Cause and the Mechanism of Their Production

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THE diastolic murmurs of aortic insufficiency are usually soft and blowing in quality, but occasionally they may be strikingly musical and very loud. Their musical quality is suggested by the various descriptive terms that have been applied to them: "cooing of a dove," "buzzing of a saw," "like a cuckoo clock," "humming of a top," etc. It is also shown by recorded heart sounds in which the vibrations are very rapid and regular (Fig. 1). Their intensity is indicated by the fact that the murmurs are often audible to the patient himself and, not infrequently, to the unaided ear of the examiner at some distance from the patient.

These loud, musical, diastolic murmurs have interested clinicians and pathologists for more than one hundred years. So far as we can discover, they were first fully discussed by Hodgkin,[1] who attributed them to retroversion of an aortic leaflet. Recent observers, with one exception,[2] have largely discarded this and other old explanations and have come to regard a ruptured or torn leaflet as practically the only, or at least the usual, cause of these murmurs. In eleven current textbooks, this is the only explanation advanced; in only one[2] is retroversion mentioned. We have recently had the opportunity of studying eleven patients who presented these unusual signs and have come to the conclusion that although a rupture or tearing away of a valve leaflet from its commissural attachment can produce these murmurs, this lesion is rare; and that the distinction of being the commonest cause should be accorded to the lesion first clearly described by Hodgkin,[1] and recently again referred to by Scott,[2] namely, retroversion or eversion of a valve leaflet.*

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*We are using the terms "retroversion" and "eversion" of a valve leaflet synonymously. By either of them, we imply that, at some point distal to the attachment of a leaflet to the aortic wall, pathologic processes have caused the distal portion of the valve to become bent downward toward the chamber of the left ventricle (Fig. 2). This is perhaps best illustrated by a longitudinal section through such a leaflet (Fig. 3).

The literature dealing with ruptured aortic valves was reviewed by Howard[3] as recently as 1928 and will not be further discussed. We wish to cite certain other papers dealing mainly with other causes of musical diastolic murmurs.

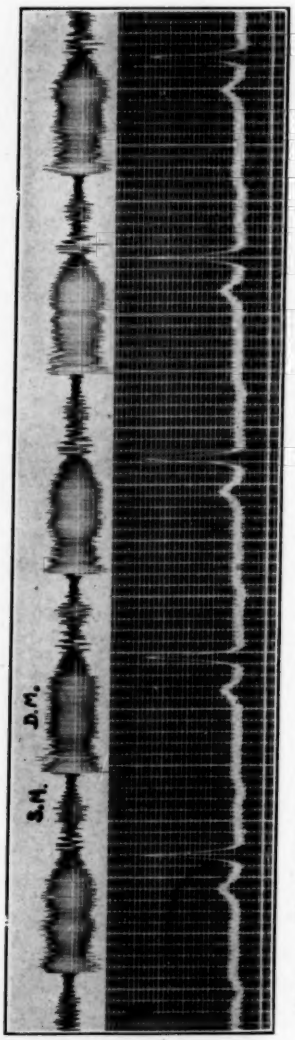

Fig. 1.—Phonocardiogram of a musical diastolic murmur. The diastolic murmur begins immediately after the second sound and continues to the first sound. This is followed by a nonmusical systolic murmur. The vibrations are quite regular and rapid (275 per minute) during most of the diastolic murmur. Toward the end of the murmur, the frequency and intensity diminish.

As we have indicated, the earliest complete discussion of these murmurs that we have discovered is contained in a paper written by Hodgkin in 1829 in which these loud diastolic murmurs are referred to as the "Bruit de scie," and likened to the "cooing of a dove." A necropsy study in one case revealed retroversion of one or two aortic valve leaflets, which was accepted as the cause of the murmur. In this paper, Hodgkin gave credit to Key for first pointing out this

lesion and its significance in 1827. Elliotson,[4] in 1830, stated that he convinced Hodgkin that Bertin[5] had first described retroversion. Neither Bertin nor Elliotson, as far as we can determine, definitely associated retroversion with musical aortic diastolic murmurs as Hodgkin did; Elliotson, however, did describe very loud musical murmurs "exactly resembling the cooing of a dove," but he attributed them to mitral lesions.

Hope,[6] in 1842, felt that loud musical murmurs were not uncommon. He found them associated both with aortic insufficiency and mitral lesions. Peacock,[7] in 1854, described a very loud, musical, diastolic murmur in a man 65 years old, which "exactly resembled the sound

Fig. 2.—Everted aortic valve leaflet. Note retroversion of the right anterior leaflet (Case 3).

produced by the common cuckoo clock" and could be heard at a distance of several feet from the patient. At necropsy, the aortic valves were thickened, the segments were separated from each other (probably syphilitic?), and the free edge of the right leaflet was retroverted. The loud musical murmurs described by Stokes[8] (1855), Wunderlich[9] (1855), and Banks[10] (1857) may have been of the type we are discussing, although their written descriptions leave some uncertainty. Stokes found the murmurs associated with irregular ossification of the aortic orifice; Wunderlich attributed them to an anomalous cord between the ventricular wall and septum, which was put on tension during ventricular filling; and Banks attributed the murmurs

to cribriform aortic valves (one case) and an atheromatous prolongation more than an inch in length, which, stretching up into the aorta, "must have vibrated like the tongue of a Jew's harp" (one case).

More recently, Wilson and Jamieson[11] (1918) studied clinically three cases of loud, musical, aortic diastolic murmurs. Two patients gave histories of having been rendered unconscious by the explosions of shells; but, since the murmurs did not become audible until a considerable time later, it was impossible to connect the accidents with the valve lesions. In neither case was there any history or evidence

Fig. 3.—Longitudinal section through aortic leaflet, which is everted (from Case 4). The leaflet is typically everted. Note interruption of the ventricularis elastica and eventual total destruction at point of eversion. V.E., ventricularis elastica; X., loss of elastica in thickened everted leaflet; A., postinflammatory scar tissue. (The fibrosa is irregularly thickened.)

of organic disease which might have weakened the valve. The third patient became conscious of the murmur on the fourth day after being gassed with phosgene, but there was no history of injury or concussion. The valve lesion in this last case was considered by the authors to be of syphilitic origin. The murmurs were all sufficiently loud to be audible to the patients themselves and to the unaided ear of the examiner one to five feet from the chest wall. Since no necropsy examinations were made, no more definite causes of these murmurs could be established.

As we have already stated, Scott, alone of the recent authors, so far as we are aware, has attributed loud musical diastolic murmurs to retroversion of an aortic valve leaflet. He referred to this lesion and to rupture of a valve leaflet as causes of these murmurs. He did not emphasize, as we believe it deserves, that retroversion is the predominant cause of these striking signs.

Clinical and Necropsy Findings.—Of the eleven patients constituting our series, five were studied only in life; six were studied both clinically and at necropsy. The essential findings are summarized in Table I. Some of the facts which require emphasis follow.

The etiology of the aortic insufficiency in all of the necropsy cases was syphilis, for in all there were characteristic aortitis and separation of the commissures. In four of the five patients studied only in life, syphilis seemed to us to be clearly the cause of the aortic insufficiency. In the remaining patient, a boy 11 years of age, the murmur developed during a typical attack of rheumatic fever and was apparently the result of this disease. In the latter patient, bacterial endocarditis was considered as an etiologic factor, but this appeared unlikely after three negative blood cultures and an afebrile course of 2 months.

In every necropsied patient, the right anterior aortic leaflet was retroverted; the posterior leaflet, as well, was retroverted in one (Case 5).

The diastolic murmur in all instances was similar, in that it was musical and loud. Such descriptive terms as the "buzzing of a saw," "cooing of a dove," "humming of a top," etc., quite aptly describe the musical character of these murmurs. While loud, the murmurs were not audible at any distance from the chest wall except in one instance (Case 1), in which the patient's bedfellow was considerably annoyed by the unusual and constant noise. The murmurs were, however, audible to the patients themselves in four instances (Cases 1, 7, 9, and 10). Incidentally, the intensity of the murmur does not necessarily determine whether it will be audible to the patient, for some of the loudest murmurs (to the examiner) were not audible to the patient, and vice versa.

All eleven patients presented marked diastolic thrills. These were of maximum intensity in the second right intercostal space in all but one instance; in Case 5, the thrill could be felt only in the third left intercostal space. It may be of some importance that the posterior, as well as the right anterior, leaflet was retroverted in this patient.

The peripheral signs in all instances indicated free aortic regurgitation. In ten of the eleven cases, there were precordial pain, congestive heart failure, or both. The manifestations were those of severe heart disease, and this diagnosis was substantiated by the outcome, for nine of the patients died while they were under observation in the

hospital. Death was sudden in several instances; usually, however, it came after a rather prolonged period of cardiac failure which set in relatively soon after the murmur was discovered, either by the patient or by a physician.

In a few instances the murmur developed suddenly during strenuous physical effort and was accompanied by severe pain and breathlessness. In other instances the patient became aware of the murmur suddenly, but the development of symptoms, while not coming on with dramatic suddenness, followed shortly.

DISCUSSION

Causes and Etiology of Loud, Musical, Diastolic Murmurs.—From the literature, it is apparent that a number of lesions of different etiologies have at one time or another been thought to be causative of loud, musical, aortic diastolic murmurs. Our own observations lead us to feel that retroversion of the right anterior aortic valve leaflet, produced by syphilitic involvement, is by far the commonest cause of these murmurs, although occasionally some other valve lesion or a different etiologic agent may be responsible. Our reason for attributing to syphilis the predominant etiologic role lies in the fact that in only one instance have we so far found any other disease which might have been a factor.

We are of the opinion that retroversion, rather than rupture or tear of a leaflet, is the usual cause of these striking murmurs, for these reasons: (1) In every patient with a loud, musical, diastolic murmur who came to necropsy, retroversion of the right anterior aortic leaflet was present and was the only constant valvular deformity that furnished a reasonable explanation of the unusual murmur; (2) tear or rupture of a leaflet, generally accepted as the cause of loud, musical, diastolic murmurs at the present time, is, in our experience, a very rare lesion. From 1931 through 1936, 10,100 necropsies were performed at the Philadelphia General Hospital. Except when bacterial endocarditis was present, this material yielded only one example of a torn or ruptured aortic leaflet; the valve leaflet showing this lesion was also retroverted.

It is to be noted that the murmurs in our patients, while sufficiently loud to dominate all other auscultatory findings, were not as intense as some that have been described, because they were not audible at a distance from the patient. It occurs to us that very loud murmurs, such as those described by Wilson and Jamieson,[11] for instance, may be the result of some lesion other than retroversion, possibly a torn or ruptured valve leaflet. Our material furnishes no definite data concerning the very loud basal diastolic murmurs. It does indicate, however, that moderately loud, distinctly musical diastolic murmurs have as their predominant cause retroversion of a syphilitic aortic valve leaflet.

Mechanism of Retroversion.—We have had an opportunity of studying histologically only two retroverted valves. There were two changes present in both which probably contribute to the development of retroversion. The first was the characteristic separation of the commissures, which might promote retroversion by permitting the free edge of the leaflet to sag and thus become more susceptible to the regurgitant column of blood. The second was a change in the fibrosa, with loss of the compactly arranged collagen fibers and thickening of the leaflet by inflammatory tissue (Fig. 4). While it is not improbable that both of these alterations may contribute to retroversion and may even be necessary preliminary changes, it seems doubtful if these lesions alone always produce the deformity, for we see both changes in uneverted syphilitic valves, although it is our impression that the fibrosal lesions were more marked in the two retroverted valves which we have had an opportunity of studying histologically than in uneverted leaflets (Figs. 3 and 4).

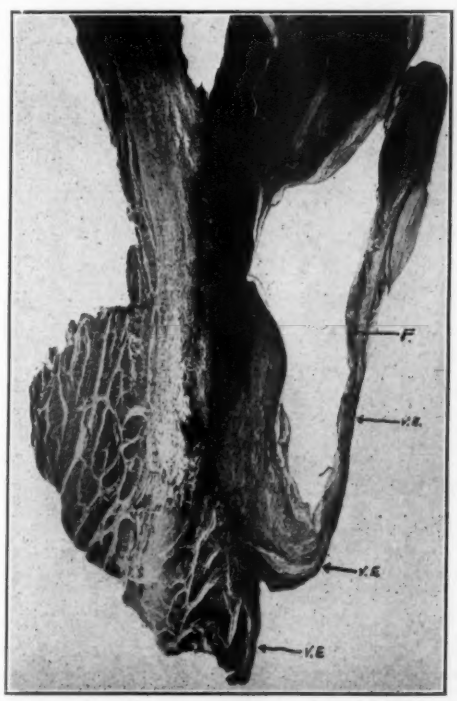

Fig. 4.—Longitudinal section through aortic leaflet, without eversion. (From a case of typical syphilitic aortitis and valvulitis). Note continuous black line of ventricular elastica sweeping up on the ventricular surface of the proximal half of the aortic leaflet. While not as thick as in the normal leaflet, it is uninterrupted, and the contour of the leaflet practically normal (Weigert's stain). V.E., ventricularis elastica; F., fibrosa.

It seems probable, therefore, that there are other factors in the pathogenesis of retroversion. One such factor has been proposed by Scott,[2] who observed a thick, tense, fibrous band running the length

TABLE I

CLINICAL AND PATHOLOGIC FINDINGS IN ELEVEN CASES OF AORTIC INSUFFICIENCY WITH LOUD, MUSICAL, DIASTOLIC MURMURS

CASE NO.	COLOR, AGE, SEX	SYMPTOMS AND THEIR DURATION	PHYSICAL SIGNS	MURMUR AUDIBLE TO PATIENT	BLOOD PRESSURE	WASSERMANN REACTION	INTERVAL BETWEEN RECOGNITION OF MURMUR AND FINAL OUTCOME	FINAL OUTCOME	NECROPSY FINDINGS OR CLINICAL DIAGNOSIS
1	B., 39, M.	Dyspnea on exertion; substernal pain; "noise in chest." (6 wk.)	Loud, musical, diastolic murmur (and thrill).	yes	150/55	4+	10 wk.	Died with bronchopneumonia	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
2	W., 43, M.	Dyspnea at rest; edema. (3 mo.)	Loud, humming, diastolic murmur (and thrill); signs of congestive failure.	no	148/20	4+	4 wk.	Died suddenly.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
3	B., 59, M.	Dyspnea at rest; edema; precordial pain. (6 mo.) (Evidences of paresis.)	Loud, musical diastolic murmur (and thrill); signs of congestive failure.	no	170/80	4+	4 wk.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
4	B., 40, M.	Dyspnea at rest; edema. (1 yr.)	Loud, musical diastolic murmur (and thrill); evidences of congestive failure.	no	170/80	neg.	5 mo.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with aortic insufficiency, eversion of the right anterior leaflet.
5	B., 35, F.	Orthopnea; anasarca. (1 yr.)	Loud, musical, diastolic murmur (and thrill); signs of marked congestion.	no	170/20	neg.	3 wk.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with insufficiency, eversion of the right anterior and posterior leaflets.

TABLE I—CONT'D

6	B., 32, M.	Dyspnea at rest; edema. (3 mo.)	Loud, musical, diastolic murmur (and thrill); signs of congestive failure.	no	170/70	4+	9 wk.	Died with congestive failure.	Necropsy diagnosis: Syphilitic aortitis with insufficiency, eversion of the right anterior leaflet.
7	B., 32, M.	Dyspnea and precordial pain on exertion; noise in chest; onset during pneumonia. (3 yr.)	Long, loud, musical, diastolic murmur (and thrill); no evidences of congestion.	yes		4+	3 yr.	Improved; left hospital.	No necropsy. Clinical diagnosis: Syphilitic heart disease with aortic insufficiency.
8	W., 46, M.	Dyspnea on exertion; and particularly precordial pain. (2 mo.)	Loud, musical, diastolic murmur (and thrill); no signs of congestion.	no	160/40	4+	10½ mo.	Died suddenly.	No necropsy. Clinical diagnosis: Syphilitic heart disease with aortic insufficiency.
9	B., 52, M.	Dyspnea at rest; hemoptysis; edema; precordial distress; noise in chest. (8 mo.)	Loud, musical, diastolic murmur (and thrill); evidences of congestion.	yes	170/60	4+	9 wk.	Died with congestive failure.	No necropsy. Clinical diagnosis: Syphilitic heart disease with aortic insufficiency.
10	B., 48, M.	Dyspnea at rest; precordial pain; hemoptysis; paroxysmal dyspnea; noise in chest. (6 wk.) (Onset sudden, while walking.)	Extremely loud, musical, diastolic murmur (and thrill); no evidences of right ventricular failure.	yes	180/60	neg.	5½ mo.	Died with left ventricular failure.	No necropsy. Clinical diagnosis: Syphilitic heart disease with aortic insufficiency.
11	B., 11, M.	Typical picture of acute rheumatic fever without striking heart failure. Three blood cultures, negative. (Under observation for 2 mo.)	Loud, musical, diastolic murmur (and thrill) developed one month after rheumatic fever was recognized; mitral valvulitis also. No congestive failure.	no	112/40	neg.	2 mo.	Improved; left hospital after being afebrile for some weeks.	No necropsy. Clinical diagnosis: Rheumatic mitral stenosis and insufficiency, and aortic insufficiency; slight cardiac enlargement.

of retroverted leaflets parallel to the free margin; he suggested that this might produce eversion by acting in a sense as a fulcrum, over which the free edge of the leaflet, distal to the fibrous band, might be bent backward toward the left ventricular cavity by the regurgitant column of blood. In some of our cases there was such a dense fibrous band. In others, although the band was present, it was not dense or tight and looked as if it might have been caused by a heaping up or wrinkling of the endocardium which developed secondary to, and not preceding, the retroversion. Other examples, notably in the two cases in which the leaflets were studied histologically (Fig. 3), showed no trace of a longitudinal fibrous band.

We wish to suggest another possible factor that may contribute to retroversion, namely, loss of the support normally furnished by the elastica. In normal aortic valve leaflets, the elastica can be traced in an unbroken line from the upper part of the left ventricle almost to the free margin of the leaflets. It lines the entire undersurface of the leaflet and is firmly attached at the commissures, thus forming a sort of sling which supports the leaflets and probably aids in maintaining their normal shape and contour. In the uneverted syphilitic valves that we have seen histologically, the elastica was still largely intact (Fig. 4); in the two retroverted leaflets studied histologically, the elastica was entirely absent (Fig. 3). Since we have studied only two retroverted leaflets histologically, we, of course, cannot say that the elastica is always destroyed in retroverted leaflets. We can say that it may be, and that, when it is absent, a leaflet will have lost one of the structures that probably aids in maintaining its normal structure.

We do not wish to draw any conclusions as to the mechanism of retroversion from such meager material, except to say that it seems not unlikely that a number of factors may contribute. We have introduced this somewhat hypothetical discussion mainly to point out the destruction of the elastica in the two cases studied histologically.

SUMMARY AND CONCLUSIONS

1. The diastolic murmur of aortic insufficiency may have a strikingly musical quality and may be quite loud. The report of a series of eleven patients* with such unusual murmurs is presented and discussed.

2. In the six patients who came to necropsy, syphilis was the cause of the aortic insufficiency. In five of the remaining patients, the clinical etiologic diagnosis was also syphilis. In one patient, a boy 11 years of age, the etiology was rheumatic fever.

3. Retroversion of the right anterior aortic valve leaflet, rather than the usually assigned cause, i.e., rupture or tear of an aortic

*Since the original series of 11 patients was collected, 3 additional patients presenting loud, musical, diastolic murmurs have been studied both clinically and at necropsy. All three showed syphilitic aortic insufficiency with retroversion of the right anterior valve leaflet.

leaflet, is emphasized as the commonest cause of loud, musical, aortic diastolic murmurs. This lesion, first suggested as a cause by Hodgkin, in 1829, was present in the six patients of our series who came to necropsy.*

4. The mechanism by which retroversion is produced is discussed.

We wish to express our great appreciation to the chiefs upon whose services these patients were studied, and to the pathologists who performed the necropsies, for permission to report these observations.

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*See footnote on page 492.

Department of Clinical Reports

QUINIDINE IN THE TREATMENT OF BENIGN AURICULAR FIBRILLATION WITH REPEATED EMBOLI*

Report of a Case

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THE indications and contraindications for the use of quinidine in auricular fibrillation have been subjected to several changes since the drug was first introduced, in 1918. The present position is perhaps most representatively stated by White,[1] who considers the patient with auricular fibrillation a possible candidate for quinidine therapy if he has no congestive failure, serious heart disease, or history of embolism. Kerr[2] adds that the drug should not be used if the underlying condition is such that restoration of normal rhythm would not improve the condition of the patient.

Recently, we have had a patient with chronic auricular fibrillation of uncertain etiology, whose only symptoms were those of repeated emboli. The question arose whether quinidine should be used to convert the rhythm to normal, with the idea of preventing subsequent emboli. The chances of a subsequent disabling or fatal embolus with the conservative treatment which was being employed were weighed against the chances entailed in the conversion to normal rhythm with quinidine. Three emboli in the systemic circuit had occurred within five weeks, two of them when the patient was at rest in bed, with no evidence of cardiac failure, and with a well-controlled ventricular rate (digitalis). It was, therefore, deemed justifiable to attempt to eliminate the auricular fibrillation.

A review of the literature was made to evaluate the risk of quinidine therapy. It is fairly well established that the drug restores normal mechanism in about 60 to 65 per cent of the cases (Wolff and White,[3] Campbell and Gordon,[4] Fahr[5]), and that the probabilities of success are greater in individuals with auricular fibrillation of short duration and little evidence of organic cardiac disease (Wolff and White,[3] Campbell and Gordon[4]). The degree of risk involved in attempting to convert the rhythm is not universally agreed upon, since this is likely to be interpreted in terms of the untoward results in one's own

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experience. The early reports dealing with quinidine (Herrmann and Wilson[6]) emphasized the danger of embolism when the drug was used in auricular fibrillation. However, subsequent studies (Viko, Marvin, and White,[8] Parkinson and Campbell,[9] Levy,[10] Cookson[11]) showed that embolic accidents were no more frequent with quinidine than with digitalis therapy. Fahr[5] states that the risk of embolism has been distinctly overemphasized. Apparently the frequency of such accidents, as well as sudden death, in the natural history of this arrhythmia has not been fully appreciated. Emboli do occasionally occur after quinidine therapy, and the chronologic relationship suggests the possibility of cause and effect. In many cases, however, the relationship is not clear.

The importance to be attached to previous emboli as a possible contraindication to quinidine therapy has not been sufficiently evaluated. It is usually stated that such an occurrence is a contraindication. However, there has been no clear evidence to show that the frequency of emboli following quinidine therapy is greater in patients with a history of embolism. Instances in which quinidine was given without mishap to patients who previously had shown embolic phenomena are cited by Clark-Kennedy,[12] Oppenheimer,[13] Campbell and Gordon,[4] and Parkinson and Campbell.[9] The last-named authors were successful in restoring normal mechanism in a patient who had mitral stenosis, a large heart, and auricular fibrillation of five years' duration, and had had three hemiplegic episodes within the preceding two years. Five years later the patient was well and vigorous, with a sinus rhythm. They point out that the return to sinus rhythm may prevent the circumstances which lead to the formation of auricular thrombi.

More important than the risk of embolism is the toxic action of quinidine on the myocardium. Sudden death has been reported with the use of the drug, but only rarely has the cause been embolic (Hay,[7] Viko, et al.,[8] Parkinson and Campbell[9]). Korns[14] found that experimental quinidine poisoning resulted in death due to ventricular fibrillation in dogs, and to standstill of the entire heart in guinea pigs. Kerr,[15] and also Davis and Sprague,[16] have described ventricular fibrillation in patients following the use of quinidine. Wolff and White[3] noted auricular standstill, with a shift of the pacemaker to the A-V node, in two patients after quinidine administration. Since the ventricle is also depressed by quinidine, they suggested that cardiac standstill may have been the cause of some of the reported cases of sudden death. However, we have not been able to find any instance in which this was proved. Clark-Kennedy[12] noted the appearance of new cardiac symptoms or the aggravation of already existing ones in seven out of eight cases in which quinidine failed to restore normal rhythm. The fact that the few autopsies which have been performed in the cases of sudden death have rarely disclosed the cause of death favors

the view that ventricular fibrillation or cardiac standstill may have been responsible. There is also the possibility of respiratory paralysis, which is the cause of death in cats (Gordon, Matton and Levine[17]).

Analysis of the literature indicates that the most serious risk with quinidine therapy is the myocardial toxicity of the drug, and that the danger of embolism, while real, has been overemphasized. The danger of serious myocardial poisoning in our patient was small, since he had no evidence of cardiac embarrassment and only slight enlargement of the heart.

The risk of forming emboli seemed to be but slightly greater than that already present; thus we felt that quinidine could be used provided careful clinical and electrocardiographic control was observed during the treatment. The drug was given to restore normal rhythm and to eliminate the underlying factors which favored the formation of auricular thrombi. This was done successfully; normal sinus rhythm was restored and maintained. No further emboli have occurred in eight months.

CASE REPORT

The patient, a 49-year-old, white, married tailor, entered the Michael Reese Hospital on the service of Dr. Sidney Portis, June 29, 1938, with acute embolism of the right brachial artery of forty-eight hours' duration. He had suddenly developed pain in the center of the antecubital fossa, which had gradually increased in intensity and had been followed by coldness and cyanosis of the forearm.

The patient first discovered that he had heart disease six years earlier, when a physician whom he consulted for an incidental complaint told him that his heart was irregular. During these years, the patient was seen twice on the surgical service, and both times auricular fibrillation was noted. There was a history of two episodes in the preceding three years which may have been embolic in nature. The first was characterized by sudden numbness, weakness, and paresthesias of both feet, especially the right, lasting thirty minutes. The second occurred a year before admission and was characterized by sudden dimness of vision, lasting ten minutes. Aside from these, the patient has had no symptoms of any nature which might be related to the cardiovascular system. He gave no history of rheumatic fever, hypertension, thyrotoxicosis, syphilis, or nephritis.

On examination, the patient was of sthenic build, had an anxious expression, and complained of pain, coldness, and numbness in the upper right forearm. The only positive findings were those related to the embolus and to the cardiovascular system. Ophthalmoscopic examination showed arteriosclerotic vessels. There were no signs suggesting hyperthyroidism. The lungs were completely negative. A faint systolic murmur was heard both at the apex and base, loudest at the apex. No cardiac enlargement could be detected, and no diastolic murmurs were heard. The heartbeat was grossly irregular, with a ventricular rate of 110 per minute and a pulse deficit of 30. The blood pressure in the left arm was 130/80. Neither the liver nor spleen was palpable. The lower extremities showed no edema, cyanosis, or clubbing. There were no petechiae.

The right arm showed slight swelling and tenderness just below the bifurcation of the brachial artery, and the right forearm was cold and blue. The right radial pulse was not palpable.

Dr. S. Perlow found that both popliteal pulses were but faintly palpable, and that neither the dorsalis pedis nor the posterior tibial pulse could be felt in either leg. Buerger's test was negative in both legs. The oscillometric indices were normal for both thighs, but were diminished in both legs.

The urine was normal, and there was no anemia. The serologic reactions were negative. The nonprotein nitrogen and sugar content of the blood were normal, as was the basal metabolic rate. Repeated agglutination tests and three blood cultures were negative.

A roentgenogram of the chest showed a slightly enlarged left ventricular shadow, with a contour of the aortic type. The cardiothoracic ratio was $\frac{17.7}{35.0}$ cm. The lungs were negative. Fluoroscopic examination confirmed these findings and showed no enlargement of the pulmonary conus or the left auricle in the oblique views. The esophagus was not displaced.

The electrocardiogram showed auricular fibrillation with a ventricular rate of 100, left axis deviation, ventricular extrasystoles, an upright T_1 and T_2, and a small, inverted T_3. The chest leads were normal.

The diagnosis rested between coronary sclerosis and rheumatic heart disease with mitral insufficiency or aortic stenosis. The sclerotic changes in the retina and in the lower extremities seemed to favor the former.

The patient was put to bed and treated with papaverine; digitalis was used to slow the ventricular rate. The arm gradually improved, the tenderness lessened, and the color became more normal, but weakness of the grip persisted. A week after entry (July 9) he was awakened by sudden pain in the right thigh, with numbness and coldness of the foot. The pulsation in the right femoral artery was markedly diminished, and the foot was cold and blue; it was thought that he had a small femoral embolus. These symptoms gradually abated, the femoral pulse returned to normal in a few days, and the patient was apparently doing well. A month later (August 8) he developed identical symptoms and signs on the left side. These also subsided uneventfully, but the left femoral pulse only partially returned to normal.

It was at this time that we decided to use quinidine. The ventricular rate was 70 per minute, and the maintenance dose of digitalis was continued. After a test dose of quinidine to rule out idiosyncrasy to the drug, the dose was gradually increased until he received 0.4 gm. every four hours, day and night. On the second day on this dose, after a total of 12.0 gm. had been given, sinus rhythm returned (Aug. 25). He was kept in bed for three days, and the dose of quinidine was gradually reduced to 0.2 gm. four times a day, for maintenance.

Following the restoration of the normal rhythm, the faint systolic murmur previously noted became much louder and harsher, but no diastolic component could be heard. Teleoroentgenograms showed that the heart was smaller and normal in size and contour. The cardiothoracic ratio at this time was $\frac{15.2}{33.0}$ cm. No significant changes in blood pressure were noted. The electrocardiogram showed sinus rhythm with a P-R interval of 0.20 sec. and a rate of 64 per minute. The left axis deviation previously seen was no longer present. $S\text{-}T_1$ and $S\text{-}T_2$ were slightly depressed, and $S\text{-}T_4$ (CF_4) was depressed. The T waves were upright in all leads. It was thought that these changes may have been due to quinidine.

Since leaving the hospital, the patient has been seen frequently by his physician (Dr. S. Perlow), who reports that he has remained well; he has had no symptoms of cardiac embarrassment and no further emboli. An electrocardiogram taken in March, 1939, showed sinus rhythm.

The patient re-entered the hospital in May, 1939, with fever, dyspnea, and weakness. Paroxysmal auricular fibrillation developed shortly after entry, but this was

abolished by increasing the dose of quinidine to 0.4 gm. four times a day. He died a week later, before a definite diagnosis had been made. Permission for an autopsy could not be obtained.

DISCUSSION

The striking feature of the case was the fact that over a period of at least six years, during which auricular fibrillation was known to have been present, the only manifestations of cardiovascular disease, other than the arrhythmia (of which the patient was unaware), were repeated emboli. At least three, and possibly five, embolic accidents had occurred within the three years prior to entry; three occurred within five weeks of observation. Following the third embolus, it was felt that subsequent emboli, one of which might be serious or fatal, were not unlikely. A careful review of the literature suggested that the major risk in the use of quinidine was the direct myocardial toxicity of the drug, which was responsible for most of the reported fatal accidents, and that the incidence of emboli with quinidine was no greater than might be expected with conservative digitalis therapy. The absence of synergic auricular contractions appeared to be the underlying mechanism responsible for the formation of mural auricular thrombi. The frequency and widespread distribution of the emboli made it advisable to abolish the conditions favoring thrombus formation, if possible, more especially because the prognosis was otherwise very good. After weighing the risks, quinidine therapy was instituted and normal rhythm restored. The subsequent course has been satisfactory in that sinus rhythm has been maintained up to the present (eight months), no further emboli have occurred, and the cardiac state has continued excellent.

Our experience in this case suggests that when a patient has auricular fibrillation, repeated emboli, and a good myocardial function and life expectancy, serious consideration should be given to the possibility that quinidine may re-establish normal auricular activity and diminish the likelihood of further emboli. If the hazard when untreated is considerable, and the benefits to be gained are many, the therapeutic risk may be justifiably taken.

SUMMARY

Quinidine sulfate was given to a middle-aged man with "benign" auricular fibrillation of uncertain etiology whose repeated emboli were the only manifestations of his disease. The result was satisfactory, with restoration of sinus rhythm, subsidence of embolic phenomena, and maintenance of excellent cardiac reserve. The risks and benefits of the use of quinidine in such cases are discussed.

The author is grateful to Dr. L. N. Katz for suggestions during the study and in the preparation of the report.

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SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY THE TYPE XVIII PNEUMOCOCCUS

Report of a Case

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IN ACUTE streptococcus endocarditis the infection of the heart valves is usually only incident to a general beta-hemolytic Streptococcus septicemia, associated with a recognizable extracardiac source of infection, such as wounds, mastoiditis, sinus thrombosis. *Streptococcus viridans* endocarditis, on the other hand, is primarily a valvulitis with thrombus formation superimposed on a previously damaged valve, and with the portal of entry of the bacteria into the body obscure or exceedingly questionable.

Libman has observed in his series of cases of subacute bacterial endocarditis that the *Streptococcus viridans* was the cause in 95 per cent, and the influenza bacillus in the other 5 per cent. Various students of this type of endocarditis have reported other causative organisms, but I have been unable to find any reports stating that the pneumococcus might be the etiologic agent in this slowly progressing and fatal disease. The following case report proves conclusively that the type XVIII pneumococcus may give rise to subacute bacterial endocarditis with clinical and pathologic manifestations which are indistinguishable from those observed in *Streptococcus viridans* endocarditis.

CASE REPORT

M. M., a 6-year-old white girl, had been a healthy child until she reached the age of three years, when, following a mild tonsillitis, she developed "heart trouble." For three years she had experienced dyspnea when climbing stairs, and one year previously a mitral systolic murmur had been discovered. On Jan. 23, 1939, she was seen the first time by her physician. The child had mild tonsillitis, with a temperature of 101.4° F. Other members of the family were suffering from hemolytic streptococcus throat infections at the time, so that no culture was made from her throat. Sulfanilamide was given, and after two days she was feeling as well as usual and was out of bed. A few days later she was found to have a fever ranging between 101° and 103° F., and on Jan. 30, 1939, she was admitted to the Kingston Hospital.

Upon admission the patient had no complaints but was pale and listless and had a "cafe au lait" discoloration of the skin. The tonsils were large and free of signs of inflammation. The mucous membranes were pale, and no petechiae could be found in them or in the skin or eye grounds. There was no clubbing of the fingers. The lungs were clear throughout. The heart was not enlarged. A low-pitched systolic murmur could be heard at the apex and was transmitted to the axilla. There was some accentuation of the pulmonic second sound, but no other alterations could be detected. The pulse was regular and of good quality, and the rate was 100. The blood pressure was 80/50. The liver and spleen could not be palpated, and nothing of significance could be found in the abdomen or extremities.

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Laboratory examinations revealed that the erythrocyte count was 3,840,000 and the hemoglobin 69 per cent (16.5 gm. = 100 per cent). There were 15,800 leucocytes per cu. mm., 83 per cent of which were polymorphonuclears. Slight albuminuria was present, but no erythrocytes could be found in the urinary sediment. The complement-fixation test for syphilis was negative. Roentgenologic studies revealed no disease processes in the mastoids. A teleoroentgenogram showed no increase in the size of the cardiac shadow.

Sulfapyridine was administered. After eight doses of 0.5 gram each, persistent vomiting developed, and a marked agranulocytosis was noted. The child received numerous blood transfusions. Neoprontylin therapy was attempted, but after a few small doses toxic symptoms again supervened, which necessitated the discontinuance of the treatment. The temperature ranged from 99.4 to 104° F. Daily urine examinations revealed occasionally a few erythrocytes and leucocytes. Blood cultures on six occasions were all positive for the type XVIII pneumococcus.

The organisms were isolated from the blood after 48 hours' incubation at 37° C. and grew in the pour plates with the formation of a wide zone of methemoglobin, and the organisms in the broth culture grew out in chains ranging from 6 to 200 members in length. The bacteriologic picture presented resembled that usually shown by the *Streptococcus viridans*. However, as is usual with organisms producing alpha hemolysis, the culture was examined serologically with the various antipneumococcic sera and tested for bile solubility and for ability to ferment inulin. The serologic reactions immediately classed this organism as a type XVIII pneumococcus.

On Feb. 10, 1939, the patient complained of pain in the lower part of the left side of the chest on inspiration, and at this time the spleen and liver were palpable. A few isolated petechiae were noted on the abdominal wall and lower extremities. The asthenia and lassitude became progressively more marked. On March 3, 1939, complete right-sided hemiplegia was noted, coma ensued, and the child died on March 10, 1939.

Final Clinical Diagnoses.—(1) Healed rheumatic mitral endocarditis with superimposed subacute bacterial endocarditis caused by the type XVIII pneumococcus; (2) splenic infarction; (3) right-sided hemiplegia; and (4) focal, embolic glomerulitis.

Necropsy Findings.—The heart, which was slightly enlarged, was found to be the seat of a healing rheumatic endocarditis and myocarditis. There were many recent perivascular scars in the muscle, and marked thickening of the leaflets of the mitral valve and thickening and shortening of the chordae tendineae. Small fibrous vegetations were present along the auricular aspect of the edges of both the mitral and tricuspid valves. Protruding into the auricle, and practically filling the mitral orifice, was a large, firm, friable vegetation attached to the aortic leaflet of this valve. Direct typing of the large number of cocci present by the Neufeld method revealed that these organisms were type XVIII pneumococci. Cultures of the vegetation yielded a pure growth of this pneumococcus. Extensive embolic manifestations were present. These included multiple petechiae in the skin, multiple recent and old yellow infarcts in a markedly enlarged spleen, and multiple petechiae in both kidneys, which showed, microscopically, changes characteristic of embolic nephritis.

Microscopic examination of the large vegetation on the mitral leaflet showed old thrombus material at the point of attachment to the valve, which was undergoing organization with the ingrowth of blood vessels and fibroblasts. Toward the center of the thrombus it was necrotic and contained no bacteria. Recent thrombus was present near the surface, and huge quantities of bacteria lay along the zone between the recent and necrotic thrombus material. A thin film of fresh blood clot, probably post-mortem clot, covered most of the surface of this large

vegetation. Partial destruction of the valve had occurred, and in that portion which remained there was a subacute inflammation. The cells present in the original portion of valve were chiefly mononuclears, with a few polymorphonuclear leucocytes scattered throughout this tissue. The changes observed in the valve and vegetation suggested that the bacterial endocarditis had long antedated the onset of clinical signs and symptoms.

Fig. 1.—Large vegetation on auricular aspect of aortic leaflet of mitral valve.

COMMENT

In this case of subacute bacterial endocarditis caused by the type XVIII pneumococcus the *Streptococcus viridans* would in all probability have been regarded as the causative organism had not the more recently available serologic methods for distinguishing higher types of pneumococci been employed. It is therefore imperative that in every case of subacute bacterial endocarditis the organism be subjected to serologic studies to make sure that it is not a pneumococcus. The Neufeld reaction in particular, should be employed. If this were done it is highly probable that many cases such as that herein reported would be discovered.

I wish to express my gratitude to Mr. George C. Groves for his aid in the isolation and identification of the type XVIII pneumococcus in this case.

Department of Reviews and Abstracts

Selected Abstracts

Sprenger, O.: Abstract of Meeting of Twelfth German Society of the Study of the Circulation. Ztschr. f. Kreislaufforsch. 31: 312, 1939.

E. Schütz (Münster) pointed out that the S-T deviation in the electrocardiogram is an expression of monophasic action currents from injured areas superimposed on ordinary action currents.

A. Weber (Bad-Nauheim) emphasized that the electrocardiogram gives no information concerning the mechanical activity of the heart, but shows evidence of local myocardial injury and alterations in spread of impulse. S-T deviations are symptoms, like dyspnea, but point to coronary insufficiency whether these are accompanied by infarction or not.

Büchner (Freiburg) was in accord in stating that necrosis is a late occurrence of coronary insufficiency of which the electrocardiographic changes are earlier evidence.

K. Heinrich (Bad-Nauheim) reported that the injury current potential in the frog's heart is smaller than the action current potential.

Hegglin and Nobile (Zurich) reported that in the mammalian heart warming, calcium, and digitalis shorten the monophasic curve, while hypocalcemia and quinine lengthen it. They differentiated between lengthening of the sustained plateau and decline of the monophasic curve. The former indicates a protraction of the state of maximum activation, the latter slow restitution.

Holzman (Zurich) spoke about middle wall infarction, which in the chest lead, with the electrode over the left sternum, shows the QRS entirely inverted; but with the electrode over the apex, shows a normal QRS but an inverted, peaked T.

G. Kayser and G. Unger (Bad-Nauheim) reported that mirror oscillographs instead of cathode ray oscillographs could be used in vector diagraphy.

Ter Borgh (Utrecht) reported anatomic studies in the horse and beef where injection showed that there were extensive connections in the septum between the right and left bundles, and that the Purkinje net extended into the myocardium as far as the epicardium.

Jung and Jantz (Freiburg) noted a prolongation of electrical systole unrelated to rate when potassium increases in blood as a result of paralysis. This disappears when the attack is over or when calcium is added.

A. V. Allen (Rochester, Minn., U. S. A.) spoke on sympathectomy in the treatment of hypertension.

Hildebrand (Frankfurt) found that a salt-free diet led to subjective improvement in only one-third of twenty-seven patients with hypertension upon whom this was tried.

M. Hochrein (Leipzig) considered hypertension to be divisible into an early and late stage. Since aging of arteries is accelerated by hypertension, lowering of blood pressure in the early stage is indicated. In the late stage the problem centers about the handling of the heart.

Sarre and Wirtz (Frankfurt) reported that denervation had no effect on the kidney flow or the A-V O_2 difference of animals with experimental diffuse glomerulonephritis.

Broemser (Munchen) discussed the physiology of heart failure in terms of the abnormal states of elasticity and resistance of the blood vessels and in terms of the circulating blood volume and the state of the venous circulation.

H. Gremels (Marburg)—Heart failure is due to insufficiency of energetics. Treatment can be attempted by mobilization of energy via the sympathetics or to increase its build up by vagus-insulin stimulation. Digitalis appears to cause a decreased membrane permeability of heart muscle and an increased effectiveness of normal vagus stimulation.

F. Volhard (Bad-Nauheim) presented his views on digitalis and strophanthin, namely that they decrease diastolic volume of failing heart and thus lead to increased mechanical work and efficiency. Strophanthin also increases peripheral O_2 utilization. Rest is important in heart failure and venesection is occasionally useful, as are leeches. Mercurial diuretics should be used after heart muscle has been strengthened. Dietary regime aiming to relieve edema is to be used. Starvation is advocated as a cure for high blood pressure, to be followed by absolute salt-free diet. Focal infection of tonsils should be eradicated. In certain cases, thyroidectomy is useful.

Blumberger (Düsseldorf) measured isometric contractions and ejection period of systole and advocated their use in estimating myocardial damage.

Schellong (Heidelberg) presented the changes which occur during ordinary and deep breathing in the electrovector diagram.

Parade (Breslau) reported that digitalis causes a decrease of the alkali curve after exercise, indicating that it produces an improved lactic acid synthesis in the muscles and liver.

Eckardt (Hamburg) noted that not all of early changes in circulation in diphtheria is due to vascular failure since severe damage to the heart is found in the earliest stages of diphtheria as could be demonstrated anatomically.

KATZ.

Scupham, George W., de Takats, Geza, VanDellen, Theodore R., and Beck, William C.: Vascular Diseases: A Review of Some of the Recent Literature, With a Critical Review of the Surgical Treatment. Arch. Int. Med. 64: 590, 1939.

This annual review of recent literature on vascular diseases is one similar to the one on heart disease. They are both invaluable résumés of their particular subjects.

MCCULLOCH.

Comroe, Julius H., Jr.: The Location and Function of the Chemoreceptors of the Aorta. Am. J. Physiol. 127: 176, 1939.

The extracarotid chemoreceptors of the dog have been localized by physiologic and anatomic studies in the *aortic body*, a structure fundamentally similar to the carotid body.

Both carotid and aortic bodies set up reflexes to the respiratory and vasomotor centers in response to anoxia, whether this be produced systemically by oxygen lack in the inspired air, or locally by interference with tissue oxidations.

The major role of the aortic chemoreceptors in the dog is the initiation of powerful reflexes to the vasomotor center during anoxemia. By far the greater portion of the hypertension of acute systemic anoxia is produced by aortic body reflexes; vascular reflexes from the carotid body are inconstant and relatively ineffective. The carotid body, however, usually contributes by far the greater portion of the hyperpnea of anoxemia in the dog; the aortic body component,

though invariably present, is often insignificant. In the cat the carotid chemoreceptors are relatively more important to the vasomotor response to anoxia than is the case in the dog.

The blood supply and afferent nervous pathways for the aortic chemoreceptors have been determined in the dog and cat. In the dog the blood supply is from the transverse aorta, in the cat from the coronary arteries. In both species the nerve fibers reach the vagus trunk close to (probably by way of) the recurrent laryngeal nerves.

The possibility that the McDowall reflex may result from chemical stimulation of the aortic body rather than from alterations in venous pressure has been discussed.

In view of the close functional and structural similarity to the carotid body, it is proper to use the term *aortic body* suggested by Nonidez, to designate structures now known as *paraganglion aorticum supracardiale, paraganglion of Penitschka, paraganglion aorticum supracardiale superius.*

AUTHOR.

Smith, Paul K., Winkler, Alexander W., and Hoff, Hebbel E.: Calcium and Digitalis Synergism. Arch. Int. Med. **64**: 322, 1939.

Dilute solution of calcium chloride was administered intravenously to digitalized dogs, and electrocardiograms and samples of blood were taken frequently during the course of the injection.

The electrocardiographic changes were correlated with the concentration of calcium in the serum. They were similar in every way to those of normal animals receiving calcium.

The mode of death of the digitalized animals was by ventricular fibrillation, or by arrest without fibrillation, just as in normal animals.

A comparison of the fatal dose and of the concentration of calcium in the serum at death in normal and digitalized dogs indicated that, by the type of experiment described here, the lethal effects of calcium and digitalis are neither synergistic nor even completely additive.

AUTHORS.

Keys, Ancel, and Friedell, H. L.: Measurement of the Stroke Volume of the Human Heart From Roentgenograms; Simultaneous Roentgenkymographic and Acetylene Rebreathing Experiments. Am. J. Physiol. **126**: 741, 1939.

A method is described in which the volume stroke of the human heart is estimated from measurements of the areas of the systolic and diastolic outlines of the heart in the frontal position on a roentgenkymographic film.

Roentgenkymograms were made simultaneously with acetylene rebreathing experiments. The results from twenty-five experiments on sixteen normal subjects fit the equation:

$$\text{Stroke volume} = 0.64\ (\text{Area}^{\frac{1.45}{\text{diastole}}} - \text{Area}^{\frac{1.45}{\text{systole}}}).$$

The average difference between the two methods was ±5.1 per cent and the greatest differences were +10.7 and −10.2 per cent, referred to the acetylene method as standard. Similar results were obtained with patients with circulatory abnormalities (myxedema, nephritis, hypertension) so long as no valvular defects were present.

Patients with valvular leaks (mitral insufficiency, aortic regurgitation) always have stroke volumes, measured by the kymograph, which are larger than the true stroke volume and this discrepancy is parallel to the best judgment of the leak

from clinical studies. The authors believe that comparison of results from the two methods gives a quantitative measure of the valvular defect.

It is noted that basal cardiac output as measured by either roentgenkymography or acetylene rebreathing generally is not attained until the subject has been through the procedure at least three or four times on different occasions.

AUTHORS.

Starr, Isaac, Rawson, A. J., Schroeder, H. A., and Joseph, N. R.: Studies on the Estimation of Cardiac Output in Man, and of Abnormalities in Cardiac Function. Am. J. Physiol. 127: 1, 1939.

Apparatus is described for recording the forces set up by the heart's recoil and the blood's impacts in man. The results obtained are characteristic of the subjects and easily reproduced.

When a subject lies on the table a damped vibration may be elicited which has a different frequency from that inherent in the apparatus. This vibration is well damped but not critically damped. The resulting errors have been evaluated by applying known impacts to the body and comparing these forces with the records obtained. From these results methods of avoiding or minimizing the errors have been devised.

In a theoretical study the form of the ballistic curve has been related to the curve of blood velocity in the great arteries during systole. Abnormal curves, encountered in disease, have been derived theoretically from abnormal blood velocity curves. The same abnormalities have been produced by asphyxiating or directly damaging the heart in animal experiments.

The relation between the ballistic waves and the cardiac output has been studied empirically by comparative experiments. Early in this work we demonstrated that there was significant correlation between them. Later the theoretical study provided formulas for cardiac output in terms of certain aspects of the ballistic waves, the aortic cross section area, and the pulse rate. When these formulas were used great improvement in the correlation resulted, the cardiac output calculated from the ballistic waves showing satisfactory agreement with that estimated by the ethyl iodide method in twenty-eight of thirty consecutive cases.

When the ballistic curve has a normal form, there is ample evidence that the cardiac output can be estimated from it with reasonable confidence. But, where the form of the ballistic record is abnormal, different formulas must be employed and, because such patients are hard to find and often very sick, evidence for the correctness of these formulas is still meager.

The ballistocardiogram seems particularly suited for estimating changes in the cardiac output of single individuals.

From the point of view of both the subject and the operator this method is the simplest, easiest, and most rapid means of estimating the cardiac output that has been proposed. A purely mechanical device, it has been in daily use for three years without trouble of any kind.

AUTHORS.

Atlas, Lawrence N.: Oscillometry in Diagnosis of Arteriosclerosis of the Lower Extremities. Arch. Int. Med. 63: 1158, 1939.

There is normally considerable variation in oscillometric readings recorded at the same level of an extremity in different persons. Of two oscillometric readings of the same magnitude taken from different persons at a given level of an extremity one may indicate a normal and the other a grossly subnormal condition.

Since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than it does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities.

The ratio of the amplitude of pulsation at the ankle to that at the wrist was between 1 and 2 in normal individuals. In patients with peripheral arteriosclerotic disease this ratio was always under one.

NAIDE.

Castex, M. R., Arana, R., Ramirez, R. L., and Battro, A.: Paroxysmal Ventricular Tachycardia. Rev. argent. de cardiol. 5: 365, 1939.

Seven cases are described of paroxysmal ventricular tachycardia with EKG records obtained during the attacks. In cases 1, 2, and 3, these were due to occlusion of the right coronary, and in case 4, to occlusion of the left one. The ventricular complex was positive in the former and negative in the latter (Lead I).

Assuming that the left coronary occlusion causes a focus of hyperirritability in the affected area or its vicinity on the anterior wall of the ventricle, apex, and anterior part of the septum, the extrasystoles, isolated or in groups, thus originated, would cause the ventricular tachycardia. According to this interpretation, ventricular complexes with initial deflexion in Lead I would originate in the right ventricle, or posterior wall of the left one, and those with negative deflexion, in the left ventricle, which is in agreement with the conclusions of Barker, Macleod, and Alexander, regarding the origin of the extrasystoles.

With the exception of case 2, the observations reported did not correspond to septal infarcts and therefore are in disagreement with the hypothesis that ventricular paroxysmal tachycardia is always the expression of a septal infarct. Pathologic examinations are needed to elucidate the question.

Of the remaining three cases one belonged to a syndrome of Stokes-Adams produced by paroxysmal ventricular tachycardia, the other to a tachycardia of Bouveret which later on degenerated to a prefibrillar tachycardia, and the third was interpreted as being ventricular tachycardia.

AUTHORS.

Perry, C. Bruce: Persistent Conduction Defects Following Diphtheria. Brit. Heart J. 1: 117, 1939.

A description has been given of three children who recovered from attacks of diphtheria with persistent conduction defects. In two this took the form of complete heart block, and in the third of bundle branch block. In all three the lesion seems to have developed at the time of their diphtheria or shortly after, and in all it has persisted for some years.

AUTHOR.

Campbell, Maurice, and Elliot, G. A.: Paroxysmal Tachycardia; Etiology and Prognosis of One Hundred Cases. Brit. Heart J. 1: 123, 1939.

One hundred unselected cases of paroxysmal tachycardia have been studied and followed for some years. In forty-two the diagnosis was confirmed by the electrocardiograph, in thirty by observation of an attack, and in twenty-eight by the history alone. The criteria of diagnosis, when this has to be made on history, have been described, the sudden onset of palpitation being the most reliable single symptom. There may sometimes be difficulty in distinguishing paroxysmal flutter and tachycardia.

Of the forty-two attacks with graphic records, eight were ventricular and thirty-four supraventricular; eleven of the latter were nodal, but in many of the other twenty-three the site of origin could not be defined more precisely. Extrasystoles were observed between attacks in twenty-one but were only of minor assistance in predicting the type of the attack. Ventricular paroxysms were very uncommon without serious heart disease.

There were forty-one of these cases with heart disease, nineteen rheumatic, two syphilitic, eight hyperpietic, and twelve myocardial. There was no heart disease other than the arrhythmia in fifty-nine, though four of these had a goiter.

The rate was between 160 and 200 in nearly half; it was between 140 and 240 in 90 per cent, but occasionally outside this wide range. There was no great difference between the various etiological groups. Nodal attacks tended to be a little slower and ventricular attacks were rather more often above 190, but even above this rate ventricular attacks formed a small minority.

Paroxysms are generally of short duration, lasting for hours rather than for days. In sixty-one the customary duration was less than two hours, and in another twenty-eight twelve hours or less. There were four where it was about twenty-four hours, and only seven where it was longer than this. But eighteen others, making twenty-nine in all, sometimes had attacks lasting more than one day, viz., over twenty-four hours, ten cases; two or three days, eight cases; up to seven days, four cases; up to ten days, five cases; and two to four weeks, two cases. One-third, therefore, of our patients had some attacks lasting more than a day, 10 per cent rarely, 10 per cent often, and 10 per cent habitually. Long attacks included an undue proportion of the ventricular paroxysms and were more common in those with myocardial disease.

Paroxysmal tachycardia is a symptom rather than a disease. In a minority of patients it accompanies serious heart disease, when, of course, the prognosis is grave. Such cases are nearly always under observation for their heart disease before the onset of paroxysms. Ventricular paroxysms form a fairly large proportion of this group and are rare otherwise. In most patients paroxysmal tachycardia is not in itself of any grave significance. It is due to reflex causes more often than to any primary change in the heart muscle. This applies not only to the majority whose hearts are otherwise normal but also to most of those with rheumatic heart disease and to some of those with other myocardial disease.

There is no close association between paroxysmal tachycardia and paroxysmal auricular fibrillation. In some of the rheumatic cases and less often in others, paroxysms of fibrillation may alternate with or replace paroxysms of tachycardia. In the rheumatic cases established fibrillation becomes a possibility in the near future.

The prognosis of paroxysmal tachycardia as regards life is, therefore, excellent, unless it is of the rare ventricular type, unless appearing relatively late in life it is the first indication of disease of the coronary arteries, or unless before the paroxysms have started there is already serious heart disease. Three of these patients have lived fifty years after the onset of their paroxysms, another eighteen for more than twenty years, and another twenty-six, making 47 per cent for more than ten years, and most of these are still in good health. Paroxysmal tachycardia does not produce heart disease, even when it continues throughout life, though one possible exception to this statement has been quoted. In general the prognosis depends on the condition of the heart muscle and should be decided without reference to the paroxysms. There is no constant tendency for the paroxysms to get worse as life advances, and usually some form of treatment can be found which will reduce the frequency and the discomfort produced by the attacks.

AUTHORS.

Mortensen, Vagn: On the Pathogenesis of Bundle Branch Block as Elucidated by the Elektrocardiographic Changes in Precordial Leads. Remarks on the Relation Between Bundle Branch Block and Other Preponderance Curves in Precordial Leads, and on the Relation of the Latter to Infarction Curves. Nordisk Medicin 1: 1971, 1939.

The electrocardiograms in standard and precordial leads in sixteen cases of bundle branch block are described. It is pointed out that there exists a great deal of conformity between the ventricular complexes in Lead IV_F in complete left bundle branch block (new terminology) and in Lead CF_2 in complete right bundle branch block and in curves belonging to Bayley's groups; this may suggest that curves belonging to Bayley's groups represent complete right bundle branch block.

Attention is called especially to the diminution or the absence of the R wave in Lead CF_2 in left bundle branch block. A similar configuration has been found in pronounced left ventricular preponderance. On account of these observations the hypothesis is advanced that the normal relation between the amplitudes of the R waves in CF_2 and IV_F depends on a certain normal relation between the conduction through the two ventricles, and *that the diminution of the R wave which may be found in pronounced left ventricular preponderance and especially in left bundle branch block is caused by a lesser or greater relative delay of the conduction through the left ventricle,* owing either to lesions in the conduction system or to hypertrophy of the left ventricle.

In standard leads the changes characteristic of pronounced left ventricular preponderance—that is, essentially, the curves described by Luten and Grove and by Rykert and Hepburn—were formerly explained in part by the hypertrophy of the left ventricle, partly by changes in the heart's position caused by the hypertrophy, and finally, owing to the resemblance between these curves and bundle branch block, by intraventricular conduction delay, which with the old terminology for bundle branch block must be localized to the right ventricle (Luten and Grove); still, Fahr and Mann and Weber have assumed that a possible delay of conduction had to be located on the left side. With the old terminology for bundle branch block, these causes, hypertrophy of the left ventricle and intraventricular conduction delay, could be considered from the same point of view only with difficulty.

The new terminology for bundle branch block is bringing quite new perspectives for the understanding of the preponderance curves. The plain transition between left preponderance curves and left bundle branch block (new terminology) makes it most likely that pronounced left preponderance curves are caused by a lesser degree of delay of the conduction through the left ventricle than is the case in left bundle branch block. Such a lesser degree of delay of the conduction is in most cases explainable by the hypertrophy of the left ventricle. Thus the new terminology for bundle branch block brings the different theories about the cause of preponderance curves into a more likely connection with each other than is allowed by the old terminology. Surely hypertrophy of the left ventricle is a very essential factor in most cases of pronounced left preponderance curves and the delay of conduction is then secondary hereto. But setting the relative delay of conduction as the immediate cause of the preponderance curves, it will be possible to explain also the cases of preponderance curves which are not accompanied by hypertrophy of the left ventricle. For a delay of conduction need not necessarily be due to ventricular hypertrophy but may be due to lesions in the conduction system.

Attention has been drawn to the fundamental difference between absence of the R wave in CF_2 in left bundle branch block or pronounced left ventricular

preponderance curves and absence of the R wave in anterior wall infarction. *In left bundle branch block we have to do with a diminution of the R wave, eventually a complete absence of this wave, whereas in anterior wall infarction we are dealing with the appearance of a new initial negative deflection (a Q wave) at the same time that the R wave is reduced in amplitude or possibly disappears altogether.* According to this *a remnant of the R wave in CF_3 in left bundle branch block will present itself as a small initial positive deflection, while in anterior wall infarction it will present itself as a notch in an initial negative deflection.*

It is pointed out that the remarks and considerations set forth in this paper may not apply to the special form of "left preponderance" curve (often with negative T_3) that is caused entirely by a horizontal position of the heart.

AUTHOR.

Buchbinder, William C., and Saphir, Otto: Heart Failure in Subacute Bacterial Endocarditis. Arch. Int. Med. 64: 336, 1939.

Heart failure of a fairly advanced grade was seen in eighteen of forty patients with subacute bacterial endocarditis, a clinical frequency of 45 per cent. At necropsy the various organs showed a marked degree of chronic passive hyperemia in every instance, and there were frequently accumulations of fluid in the serous sacs.

The presence of marked chronic passive hyperemia of the lungs, liver, and other viscera in twelve additional patients in whom the heart failure was not recognized clinically indicates that here, too, it must have been present for some time. The combined frequency of heart failure for the groups studied pathologically and that studied clinically was 75 per cent.

Ten patients had no chronic passive hyperemia. The clinical course of six of these was terminated by the rupture of mycotic aneurysms.

Extensive myocardial lesions are observed uniformly in patients who die of subacute bacterial endocarditis. They consist of minute emboli, infarcts and abscesses, diffuse inflammation, Aschoff bodies, and perivascular fibrosis.

These structural alterations are adequate to explain the advent of heart failure in this disease. They are of such magnitude and intensity as to make it remarkable that heart failure is not even more marked than we found it to be.

It is not necessary to invoke such general causes as toxemia or exhaustion to explain the advent of heart failure in subacute bacterial endocarditis.

The coexistence of rheumatic myocarditis and subacute bacterial endocarditis cannot be considered casual in the development of heart failure.

AUTHORS.

Volini, Italo, F., and Flaxman, Nathan: The Effect of Nonspecific Operations on Essential Hypertension. J. A. M. A. 112: 2126, 1939.

Twenty-seven patients with essential hypertension, on whom operations had been performed for reasons other than hypertension, were studied. The authors conclude that the relief of symptoms such as headache and the reduction of blood pressure were similar to and somewhat better than those obtained by specific procedures performed especially for the treatment of essential hypertension. However, the evidence presented hardly justifies these conclusions in the reviewer's opinion. It is well recognized that the blood pressure fluctuates in essential hypertension. An hourly record of blood pressure for twenty-four hours when the patient is admitted to the hospital shows that there is always marked reduction as a result of rest. Many physicians know that blood pressure is lower after operation than on admission to the hospital or to the clinic. The authors

have made no new observation in this regard, but they have done well to emphasize it. The beneficial effects of sympathectomy on blood pressure cannot, apparently, be judged by the value of the blood pressure shortly after operation and many of those who have reported their results of sympathectomy for hypertension do not even include these values for blood pressure in their presentations. The proof of value of an operative procedure in influencing blood pressure depends on whether or not the blood pressure is persistently reduced when patients return to normal activity after operation. Study of the author's data indicates that of the twenty-seven patients studied the blood pressure was significantly lower several years after operation than before in only seven instances. Each of these late blood pressure determinations was made when the patient returned to the hospital when congestive failure or other manifestations occurred, a time at which one might reasonably expect blood pressure to be lower as a result of rest and congestive failure. In evaluating the effects of any operations on arterial blood pressure it seems inadvisable to compare pressures during activity when patients were in good enough physical condition to warrant operation with those obtained later when they had congestive failure or other manifestations. The authors have performed a service by emphasizing the need for careful evaluation of results, but they have apparently committed the same error which they attribute to those who have reported results of operations on the sympathetic nervous system of patients with essential hypertension.

ALLEN.

Maher, C. C., and Wosika, P. H.: Urologic Hypertension. A Study of 101 Cases. Proc. Inst. Med., Chicago **12**: 388, 1939.

In 600 hypertensive patients, the authors found that 101 exhibited a wide variety of urologic lesions. One quarter of these (26 cases) suffered from "parenchymal renal disease such as glomerulonephritis," and the rest showed a variety of infectious and obstructive lesions. Hydronephrosis was common due to a variety of lesions. In the list of lesions were such conditions as pyelonephritis, renal stone, and even urethral stricture. The point made is that each case of essential hypertension deserves a thorough urological examination.

STEELE.

Opsahl, Roald: On the Pathogenesis of Arterial Hypertension With Especial Regard to the Role of the Kidney and Adrenals in the Mechanism of White High Blood Pressure. Acta Med. Scandinav. Suppl. xcii. 1938, 262 pp.

Part I. Physiological Regulation of Arterial Pressure

In the first few pages Opsahl records recent evidence for his premise that essential hypertension is due to a constriction of the peripheral arterioles not dependent upon nervous regulation but upon "intrinsic spasm" of the musculature. He defines the disease about which he wishes to talk ("Blutdruckkrankheit") by indirection and says, "The concept can be delimited by excluding conditions known to be or provisionally accepted as causes of hypertension. . . ." In this way he avoids the nosologic error of considering what is left as a single entity.

Beginning with Allbutt's break, in 1895, from the view of Traube that all hypertension was conditioned by renal disease, he briefly leads up to Volhard's concept of "red" and "white" hypertension, and then states his own view in the form of a working hypothesis as follows: Persistent arterial hypertension

can, he believes, be brought about by three factors: (1) A pure extrarenal one, (2) a pure renal one, and (3) a combination of the two. He believes also that a renal factor can eventually be brought about apparently as the result of hypertension due to an extrarenal factor.

With regard to hypertension due to renal disease, he urges a break with the accustomed notion of renal insufficiency and suggests the term "filtration-insufficiency" as a cause of hypertension. This can be brought about either (1) by diminished function of the glomeruli or (2) by sufficient increase in resistance in the arterioles supplying the glomeruli to diminish filtration pressure.

A long description of Volhard's "red" and "white" hypertension and "paroxysmal" hypertension (Pal's crisis) follows with excellent review of evidence from the literature for and against the underlying concepts.

Part II. Original Studies

His aim is threefold: to elucidate the relation (1) of size of adrenal glands to hypertension, (2) of their arterial blood supply to hypertension and to the state of the kidneys and (3) between basophilic infiltration of the hypophysis and hypertension. His material consists of 535 autopsies and notes of their clinical condition. To correlate these cases with the three objectives, he first relates size of heart to arterial hypertension after discarding fifty-nine cases of organic heart disease and finds the correlation good. On the basis of weight of the heart he regards 258 cases as normal, 120 as probably, and 98 as surely, hypertensive. There were found present 101 cases of renal disease (some arteriosclerotic, some chronic nephritic) with hypertension.

The three aims were achieved as follows:

1. The weight of the adrenals and blood supply were studied. He found that in 233 cases without renal disease or hypertension the mean weight was in men 12.3, in women 11.9 gm. while in cases with certain hypertension the mean weight was for men 15.3, for women 13.8 grams. That this was not due to edema was ascertained by finding that the same relation holds for the dry weights of the gland. He concludes that the increase in size of the adrenals is indicative of the existence of the chronic "emergency state" (Cannon) due to "renal infiltration-insufficiency" being compensated for by chronic arterial hypertension.

2. The form and richness of blood supply to adrenals was elaborately studied in 100 cases by injecting a suspension of barium sulphate into a freshly removed preparation of diaphragm, adrenals, kidneys, and ureters with the arterial blood supply intact and still connected to the section of the aorta from which the vessels to these organs arise. The injection was made into the upper cut end of the aorta after the lower end and all mesenteric vessels had been tied. Correlation between blood supply of the adrenals and kidney disease or hypertension was not found.

3. Clear-cut relation between basophilic infiltration of the hypophysis and hypertension was not found. The author believed that there was a greater tendency for the older age groups to show increased basophilia and that this may have been a disturbing factor in the analysis of hypertension.

The formal conclusions appear to outrun by far the original work and consist chiefly of a theoretical classification of hypertension and a hypothesis concerning mechanism of its production. Nor is there a word in conclusion about his studies on the hypophysis.

The main conclusions are:

1. Three pathogenetic mechanisms underlying chronic hypertension can be distinguished: (1) A purely constitutional one, (2) a pure renal one and (3) a combined one (constitutional hypertension "provoked" or brought out by a renal factor). The constitutional hypertension corresponds to Volhard's "red," the other two to "white" hypertension.

2. A renal hypertension is a compensatory phenomenon for relative filtration-insufficiency (not failure of the excretory function). When hypertension can no longer compensate for the *filtration*-insufficiency, then *renal* insufficiency may be said to exist.

3. The increase in size of adrenal glands agrees with the modern conception of the role of these organs in regulating arterial pressure and can be regarded as necessary for meeting the chronic emergency of renal filtration-insufficiency by compensating for it with a persistent elevation of arterial pressure.

STEELE.

Horn, Henry, Dack, Simon, and Friedberg, Charles K.: Cardiac Sequelae of Embolism of the Pulmonary Artery. Arch. Int. Med. **64**: 296, 1939.

A group of forty-two cases of embolism of the pulmonary artery has been studied, in eight of which recent structural changes in the myocardium ordinarily resulting from acute myocardial ischemia were revealed.

The factors necessary for the production of such myocardial changes are discussed. These are shock, asphyxia, and exaggerated vagal reflexes resulting from obstruction of the pulmonary arteries. These factors, alone or in association, lead to insufficiency of the coronary circulation. Morphologic evidence of coronary insufficiency in cases of embolism of the pulmonary artery is more likely to occur if there are recurrent embolization, narrowing of the coronary arteries, cardiac hypertrophy, and adequate duration of life after embolism.

Anatomic changes in the myocardium in persons with embolism of the pulmonary artery may be considered the end result of the myocardial ischemia which accounts for the characteristic electrocardiographic changes.

The resemblance of electrocardiographic changes in cases of embolism of the pulmonary artery to those in cases of myocardial infarction of the posterior wall may be explained by the diminished flow through the right coronary artery resulting from increased tension in the right ventricle.

AUTHORS.

Gregg, Donald E., Thornton, John J., and Mautz, Frederick R.: The Magnitude, Adequacy and Source of the Collateral Blood Flow and Pressure in Chronically Occluded Coronary Arteries. Am. J. Physiol. **127**: 161, 1939.

The results presented elucidate in part what happens dynamically in the vascular bed of a chronically occluded coronary artery in favorable dogs and have led to the belief that a large new collateral circulation develops. Our criteria for such a belief are the recorded experimental facts that (1) in twenty-two of twenty-three dogs the peripheral coronary pressure is greatly increased (as compared to normal controls) and at times to values even approaching aortic pressures; (2) the retrograde blood coming from the peripheral end of the occluded coronary ranges up to 105 c.c. per minute with most of the values around 30 to 40 c.c. per minute; (3) the retrograde blood is so similar to arterial blood that it cannot be differentiated on the basis of its carbon dioxide and oxygen content, and (4) such volume flows of arterial blood are sufficient for the met-

abolic needs of the potentially infarcted myocardium, for the myocardial region exhibits normal contractions except in areas of scarring.

No single pulse pattern or set of ordinate values exists in the peripheral ends of the major coronary rami chronically ligated. The most usual peripheral coronary pressure is similar in timing and contour (although greater in magnitude) to the normal curve obtained immediately after coronary ligation, others more nearly resemble an intraventricular pressure curve while less frequently the peripheral coronary pressure curve can scarcely be distinguished from the aortic curve simultaneously recorded.

From an analysis of these coronary pulse patterns the conclusion is drawn that most of the collateral flow occurs during diastole and that only in those coronary pressure curves which resemble the aortic in ordinate values and contour can the source of the retrograde blood be predicted.

By clamping the other coronaries either separately or together while measuring the retrograde flow in the third coronary chronically occluded, the functional extent of the newly established coronary anastomoses has been determined. It has been found that:

The descendens receives on an average 62 to 66 per cent of its collateral flow from the other coronaries (right 7 per cent and circumflex 55 per cent).

The circumflex receives 66 to 64 per cent from the other coronaries of which the right and descendens contribute 19 and 47 per cent.

The right receives 97 to 79 per cent of its flow from the left coronary artery, the descendens contributing 22 per cent and the circumflex 75 per cent.

This leaves a large residual flow in the left coronary and a small residual flow in the right still to be accounted for. The origin of this potential extracoronary retrograde flow has not been determined.

AUTHORS.

O'Shaughnessy, Laurence, Slome, David and Watson, F.: Surgical Revascularization of the Heart. Lancet 2: 617, 1939.

Histologic and injection studies are presented, demonstrating that vascular connections will develop between the vessels of the myocardium and extracardiac vessels (a) when cardiopericardial adhesions are produced with aleuronat; (b) when a pedicled omental graft is introduced into the pericardial sac and adhesion between omentum and heart is stimulated with aleuronat; and (c) when omentum is grafted to the outer surface of the pericardium after the production of cardiopericardial adhesions.

Collateral communication will develop between the pulmonary and coronary circulations if a lobe of the lung is grafted to the myocardium.

AUTHORS.

Flothow, Paul G.: The Surgical Treatment of Essential Hypertension. Am. J. Surg. 44: 535, 1939.

The preoperative testing and surgical treatment of patients with essential hypertension are reviewed. The results of operations on twenty-two patients are presented.

The author believes that there is no other method of treatment of essential hypertension that offers anything comparable to the results following extensive sympathectomy in selected patients. Postoperative blood pressure cannot be the only criterion of results accomplished since many patients who exhibit no fall in blood pressure are markedly improved clinically and symptomatically.

NAIDE.

Spink, Wesley W., and Crago, F. Hughes: Evaluation of Sulfanilamide in the Treatment of Patients With Subacute Bacterial Endocarditis. Arch. Int. Med. 64: 228, 1939.

It appears from the foregoing observations that the administration of sulfanilamide to patients with subacute bacterial endocarditis will in some instances render the circulating blood free of organisms. Except for two of the patients, this bactericidal effect was only temporary and depended on the continued use of the drug. In two patients definite improvement followed the use of sulfanilamide. However, we believe that sulfanilamide and its related compounds will be of doubtful value in the treatment of patients with subacute bacterial endocarditis because of the very nature of the focus of infection. The proliferating mass of bacteria situated well beneath the surface of the vegetation is probably protected, at least in part, from the action of free sulfanilamide in the blood, as well as of specific antibodies. When the organisms approach the surface of the vegetation, they are carried off in the circulating blood, and under these circumstances may be killed. An analogous therapeutic situation is now recognized in the treatment of patients with bacteremia due to beta hemolytic streptococci. Lockwood stated that in a number of instances of infection of the blood stream an infected thrombus in a large vessel has prevented satisfactory elimination of the bacteremia.

Since the presence of sulfanilamide in the blood may have a bacteriostatic effect on some strains of *Str. viridans*, sulfanilamide probably should be administered to any patient with valvular lesions who may be subjected to oral surgical procedures. It is well known that after the extraction of teeth or after a tonsillectomy temporary bacteremia with *Str. viridans* may result.

AUTHORS.

Edwards, Edward A., Hamilton, James B., and Duntley, S. Quimby: Testosterone Propionate as a Therapeutic Agent in Patients With Organic Disease of the Peripheral Vessels. New Eng. J. Med. 220: 865, 1939.

Following the treatment of human male castrates with testosterone propionate there was an increase in arterialization and blood volume in the head, palms of the hands and soles of the feet. The vascular changes in the skin were observed with the recording spectrophotometer.

Seven male patients with organic vascular disease were then treated with crystalline testosterone propionate. Three of the men had thromboangiitis obliterans and four were arteriosclerotic. All had occlusion of major vessels. Administration of testosterone propionate produced favorable changes in all the patients. The spectrophotometer curves after treatment showed an early and decided arterialization of the cutaneous blood. Other beneficial effects were relief of night pain and improvement in intermittent claudication. These findings are presented as a preliminary report.

NAIDE.

Book Reviews

CLINICAL RADIOLOGY OF THE HEART AND GREAT VESSELS: By C. H. Laubry, P. Cottenot, D. Rositier, and R. Heim, Paris, 1939, Masson et Cie.

Those who during the last year have followed the abstract section of THE AMERICAN HEART JOURNAL will have been impressed with the importance of the studies on radiology of the heart which have come from Laubry's clinic. This work has now found a fitting climax in the two volumes which have just been issued. The authors' special contributions are here included in a comprehensive atlas, comprising practically all known information on the subject. The work does not follow the standard classification of heart disease, but is logically developed along radiologic lines.

The parts which the various chambers of the heart play in the formation of the cardiac shadow are clearly illustrated by the post-mortem injections with opaque media. The various types of normal hearts are considered, including kymographic studies. Consideration is given to the variations occurring at various ages, during pregnancy, and from extrinsic factors, such as pleural effusions, pulmonary fibrosis, thoracic deformities, and diaphragmatic hernias. It is shown how normal hearts may simulate mitral lesions.

A wealth of pictures illustrates rheumatic heart disease; how mitral lesions are consistent with normal heart shadows; the evolution of the lesions through the years; and how cardiac enlargement affects the mitral characteristics. Throughout, modern concepts of heart disease are applied to the interpretations. Changes in the pulmonary circulation and the hilus shadows are also shown. Special attention is given to enlargement of the left auricle and the part it plays in the formation of the right cardiac border. The shadow of the left auricle is shown superimposed on that of the rest of the heart. The displacement of the bronchi and the esophagus is shown by contrast media. Finally pictures are shown of multiple valvular involvements, pancarditis, and aortic regurgitation.

In the second volume the first sections are devoted to congenital heart disease. Rogers' disease, alone and in conjunction with other defects, pulmonary stenosis, coarctation of the aorta (not quite so plain as the rest), persistent ductus arteriosus, patent foramen ovale, transposition, and idiopathic hypertrophy—a full catalogue.

Next, the authors turn to aortitis and the degenerative changes, arteriosclerosis and the resulting deformities, of which an amazing collection is shown, senile changes, and aneurysms in all forms and locations. The test here contains a valuable discussion of the diagnostic signs, including a kymographic discussion. Then come myocardial disease, coronary infarction, and cardiac aneurysm. Dilation of the pulmonary arteries is beautifully shown, also the effect of hypertension of long standing. Pericardial diseases are considered: effusions, adhesions, calcifications, and even a case of diverticulum. Cardiac insufficiency is illustrated including pulmonary edema during and following an attack. A few pictures demonstrate the technique of locating foreign bodies in the heart. The work closes with a collection of diagnostic problems.

Throughout, the very highest standards prevail; the photographs are as perfect as is technically possible. They show even fine shades of contrast and are beautifully reproduced. The text is condensed, yet adequate. Only one small

criticism may be leveled against the work: a considerable number of reference figures in the text have been misprinted. The volumes constitute a landmark in cardiac diagnosis and should find wide distribution.

JULIUS JENSEN.

PERIPHERAL VASCULAR DISEASES, DIAGNOSIS AND TREATMENT: By William S. Collens, M.D., Chief of the Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, Brooklyn, N. Y., and Nathan D. Wilensky, M.D., Assistant in the above clinic. 243 pages, 1939, $4.50, Springfield and Baltimore, Charles C. Thomas.

The aims of this book are presented in the preface. "This book has been planned to offer the physician a ready reference and a compendium which will aid him in the early recognition of peripheral vascular diseases and to offer him specific instruction in the management of the individual case." Since there is little or no consideration of diseases of the veins or lymph vessels, a more appropriate title would be "Peripheral Arterial Diseases." However, such a title would not be quite accurate, for aneurysm, glomus tumors, periarteritis nodosa, and arteriovenous fistula, for example, are considered minimally or not at all. The bibliography is incomplete; many important contributions are not mentioned. The term "peripheral vascular sclerosis," used to designate "peripheral arteriosclerosis," is an example of loose exposition. While the authors have attributed inflammation of peripheral arteries to syphilis, rheumatism, tuberculosis, pneumonia, and typhoid fever, they present no evidence that this actually occurs. The chapters on "Methods of Examination" and on "Symptoms and Signs of Interference With Arterial Flow" are fairly complete. The chapters in which methods of treatment are evaluated have much merit. The reviewer can offer objections to relatively minor points. Three examples follow: The few words on sympathicotonia do not clarify this elusive or nonexistent syndrome. The application of the term "nocturnal claudication" to "nocturnal cramps" serves only to confuse. Nocturnal leg cramps by no means affect only individuals with diabetes, as the authors imply. The statement is made that it is important to differentiate "peripheral vascular sclerosis" from thromboangiitis obliterans, but no reasons are given.

It is logical that the authors should devote a good deal of space to intermittent venous occlusion, a method of treatment which they originated, but it is unfortunate that comparatively little should be written of other methods of treatment which some authorities regard as more efficacious. The unfortunate intimation that the authors recently originated the test for determining the distance patients must walk to produce claudication overlooks publications of several years ago in which this test was described by others. The authors' question whether the improvement noted during treatment of thromboangiitis obliterans with repeated intravenous injections of hypertonic salt solution is not due to spontaneous regression of the disease might well be asked with respect to the use of intermittent venous occlusion.

The book is attractively printed.

EDGAR V. ALLEN.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*